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ARCHIVES OF SURGERY

VOLUME 31 OCTOBER 1935 NUMBER 4

FASCIAL SARCOMA AND INTERMUSCULAR MYXOLIPOSARCOMA

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NEW YORK

The term fascial sarcoma became established in reports in the older German literature (1850-1900) but never gained wide usage. Virchow [1] described fascial sarcoma as occurring rather frequently, especially in the superficial fasciae of the lower extremities. It was generally of fibromatous or fibrosarcomatous structure, but sometimes it was quite cellular and malignant and therefore probably of rather uncertain nature and origin. In many cases there was formation of cartilage and bone, and Virchow seems to have identified this fascial sarcoma with the so-called parosteal sarcoma. He remarked that osteosarcoma is not necessarily a bone sarcoma. He did not use the term fascial sarcoma for any of the intermuscular myxosarcomas. He fully described intermuscular myxosarcoma, occurring especially in the thigh but also in other regions where fat tissue is abundant. He did not state the exact origin of intermuscular myxosarcoma, but he noted the frequent presence of fat cells and of fat tissue in the tumor, which he seems to have regarded as the fatty degeneration of a primary myxoma. Cartilage and bone were found occasionally in intermuscular myxosarcomas, but because of this he did not identify the myxosarcoma with the true fascial tumor containing cartilage and bone.

Later authors confused intermuscular myxosarcoma with the true fascial sarcoma described by Virchow. Thus Hellmann [2] in 1888 analyzed eighty-three cases of sarcoma of the inguinal region, reporting seven cases as instances of fascial sarcoma. Six of the tumors were cellular growths of the type of myxosarcoma. They were located between the deep muscles and were attached more or less to the deep fasciae, to the muscles or to the sheaths of blood vessels. The exact origin was not determined. The other tumors of the series arose from nerve trunks, muscles, lymph nodes and miscellaneous sources. Hellmann referred the origin of many inguinal sarcomas to the sheaths of vessels.

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 2, p. 342.

2. Hellmann, L.: Ueber den Ursprungsort der Weichteilsarcome der Regio inguinalis, Würzburg, H. Stürtz, 1888.

In 1913 Massenbacher [3] reported several cases of intermuscular myxosarcoma, especially in the thigh, and referred the origin to the deep fasciae and the fascia lata. Apparently he did not recognize that the tumors were quite different in location and structure from the fascial tumors described by Virchow. Most of the cases reported in the literature to which he referred were instances of desmoid tumor of the abdominal parietes. In the recent literature, the term fascial sarcoma does not appear frequently. In the "Quarterly Cumulative Index Medicus" for the past ten years I find references to only two cases of the condition. One of these was a case of enchondroma of the subcutaneous fascia reported by Goldmann [4] in 1928. The other was a case of perithelial sarcoma of the cubital fossa above the elbow following alleged trauma described by Cooper [5] in 1930. Although the median and internal cutaneous nerves ran through the tumor, they were apparently not connected with its origin, and the author concluded by exclusion that the tumor must have arisen from the deep fasciae.

At the present time the term fascial sarcoma, if used at all, is generally applied to the intermuscular myxosarcomas described by Hellmann and by Massenbacher and to desmoid tumors of the abdominal wall and not to the fibrous, fibromatous, fibrosarcomatous or parosteal sarcomas described by Virchow. It is to this former group of myxosarcomas that the present study is directed.

Notwithstanding the paucity of reports, deep intermuscular tumors of this type are not rare. On the contrary, they form a well defined clinical group of malignant tumors of the extremities, of which the gross anatomic changes are uniform and characteristic, the structure peculiar and highly specific and the clinical course progressive and generally fatal. Surgical intervention is generally unavailing, and the therapeutic problem is therefore urgent. If a definite histogenetic orgin could be established, these tumors could be regarded as a specific neoplastic disease.

As a result of a study of many tumors of this type over a period of years and of a comparison with other deep intermuscular sarcomas in the same regions, I have reached the conclusion that the characteristic intermuscular myxosarcoma sometimes referred to as fascial sarcoma is a variety of liposarcoma in which the small blood vessels are the predominant element and in which mucous tissue, instead of fat tissue, is the product of the cell growth. This conclusion might well have been drawn from the descriptions given by Virchow and the early observers, who often noted the abundance of fat cells in a few of these tumors,

3. Massenbacher, J.: Fascien-tumoren, Beiträge z. klin. Chir. **88**:69, 1913.
4. Goldmann, D.: Zentralbl. f. Chir. **55**:2379, 1928.
5. Cooper, T. V.: Lancet **2**:1234 (Dec. 6) 1930.

but when the term fascial sarcoma came to be employed for the group, the idea of an origin from fat tissue seems to have been neglected.

POSSIBLE SOURCES OF ORIGIN OF INTERMUSCULAR MYXOSARCOMA

As possible sources of such tumors muscles, nerve trunks, muscular fasciae and fat tissue must be considered. While some myxosarcomas contain cartilage and a few others have shown bone formation, the theory of an origin from misplaced islands of periosteum seems to have no definite evidence in its support, although an osteogenic influence from the proximity of the tumor to bone might be considered as a possible, but rather intangible, explanation. The tumors are not connected with bone, and the bone shaft is not affected even by pressure, as are certain neurogenic sarcomas lying near bone. The occasional presence of cartilage and bone must be ascribed to a metaplastic process.

The possibility that the origin is from muscle must also be rejected. A myosarcoma of the skeletal muscles arises within the muscle and not between the muscles. While muscle fibers are sometimes found in myxosarcomas, this seems to occur exclusively in rare cases in which the myxosarcoma, usually encapsulated, breaks the capsule and infiltrates the skin and neighboring tissue. This event occurs only in the later stages of a recurrent tumor. The structure of the tumor also is entirely different from the large spindle cell and giant cell composition of a myosarcoma.

Neurosarcoma presents myxomatous features in a small proportion of cases, but in such cases the other features of the growth reveal characteristic signs of neural origin. On dissection, nerve trunks may be seen coursing through the myxosarcoma, but usually the nerves are readily separated from the tumor. The structure of intermuscular myxosarcoma is quite different from that of myxomatous neurosarcoma. Yet combinations of neuroma and lipoma are not extremely rare, and occasionally one encounters a malignant tumor of the nerve trunks composed of myxomatous and liposarcomatous elements. Such a growth was described by Virchow in 1857.[6]

A direct connection between the myxosarcoma and the fasciae investing the muscles I have not observed, and it does not appear to have been demonstrated in any reported case.

The fasciae investing the voluntary muscles appear in the form of strands of dense fibrous tissue radiating from the tendinous insertions and condensed into firm, tough flat bands in particular regions. Its structure is that of very dense avascular fibrous tissue resembling tendon tissue. Such tissue cannot be regarded as a ready source of any tumor process. The true fascial tumor is therefore quite rare. That any

6. Virchow, R.: Virchows Arch. f. path. Anat. **11**:281, 1857.

of the soft vascular myxosarcomas arise from true fascial tissue investing the muscles seems highly improbable and lacks any definite support. The term fascial sarcoma should be limited to the fibromas, fibrosarcomas, chondromas, osteomas and parosteal sarcomas described by Virchow and by a few later writers.

Origin from Sheaths of Vessels.—The older authors were much impressed with the evidence suggesting that some intermuscular sarcomas arise from the walls of the deep blood vessels. On surgical dissection the tumors were found to arise from a pedicle consisting of a leash of blood vessels; some were very vascular and contained cavernous blood spaces, with the multilobed mass closely adherent to the fasciae and to the walls of the vessels. Hellmann collected reports of nine cases in which the tumor was thus connected with the vessels, but the histologic details in these cases were inadequate to determine the exact nature of the tumors. He was therefore unable to establish the exact point of origin, and he quoted Langenbeck as stating that a definite indication of origin of any of these tumors from the sheaths of blood vessels could not be given. The gross description of the tumor suggests that it was really a form of myxosarcoma or liposarcoma in which the central nutrient blood vessels were unusually well defined. If the tumor arose from a lobule of fat tissue, the overgrowth of central blood vessels would explain the vascular character of the tumor and also the close connection with the sheaths of blood vessels.

Origin from Fat Tissue.—In considering the origin of intermuscular myxosarcoma from fat tissue, one must refer to the general physiology, embryology and structure of fat tissue. Schaffer [7] emphasized the close relationship of fat tissue, cartilage and chordal tissue, any one of which may substitute for or replace any other under comparable conditions, as is shown by comparative histologic study. In this connection, reference may be made to the report by Seidelin [8] of the occurrence of chordoma-like cells in a liposarcoma lying between the pectoralis major and the pectoralis minor muscle. According to Flemming, fat tissue cells arise regularly and probably invariably from fixed connective tissue cells, and fat tissue is therefore to be closely identified with connective tissue. On the other hand, Toldt separated fat tissue sharply from connective tissue and held that it is derived from well defined lobulated embryonal organs located in various regions in which fat tissue normally appears in the adult. In these organs there is a rich, peculiar and closed system of fine blood vessels in the meshes of which lie specific round granular cells without membrane which become the fat cells of adult fat tissue. The last-mentioned

7. Schaffer, J., in von Möllendorff: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1929-1930.

8. Seidelin, H.: Acta path. et microbiol. Scandinav. **9**:289, 1932.

conception is of importance in the present connection, because many types of myxosarcoma and liposarcoma have this structure and therefore lend support to this opinion. Myxosarcoma, especially, in the early stages exhibits first a striking overgrowth of fine blood vessels, arterioles and capillaries about which fat cells and mucous material develop. The cells, steatoblasts and lipoblasts, are derived from the adventitial layers of the blood vessels. They first appear as granular nucleated cells lying in the rich capillary network and producing a structure which resembles liver tissue. This structure is often suggested in cases of cellular liposarcoma.

Mucous tissue often appears in an embryonal fat anlage, the cells assuming the shape of stars and lying in a scanty mucinous matrix. This same structure is more often observed in regressing fat tissue, and it is closely imitated in myxosarcoma.

The adult fat cell is surrounded by a membrane the composition of which somewhat resembles elastic fibers. Besides fat, the cell always contains a nucleus, flattened and generally invisible in sections of the tissue. A trace of granular cytoplasm accompanies the nucleus, and in it a Golgi apparatus has been identified. In regressing and inflamed fat tissue the granular cytoplasm increases, and the nucleus enlarges, becomes visible and multiplies; thus the alveolar structure of inflamed fat, familiar to all pathologists, is produced. The same changes with granular polyhedral cells containing little fat often appear in the early stages of liposarcoma.

Histologists emphasize the existence of two kinds of adult fat: the common white fat and the less widely distributed brown fat. Brown fat is found chiefly in the mediastinum, the perirenal region and the axillae and about the thymus and the joints. The cells are large, polyhedral and granular, and they contain varying proportions of fat granules, sometimes only a few. The tissue is therefore opaque and highly colored. This structure is observed in fatty tumors and is generally designated by pathologists as xanthomatous. Yet all xanthomatous processes can hardly be considered to develop from brown fat tissue. The occasional occurrence of an orange-colored lipoma or liposarcoma, especially about the joints, kidneys and adrenals, suggests that the origin is from brown fat.

This short review of the comparative histologic and embryologic characteristics of fat tissue supports the view that intermuscular myxosarcoma is a form of liposarcoma and is derived from fat tissue. This tumor reproduces exactly the early embryonal process of fatty development by the growth of adventitial cells in a network of small blood vessels in a mucinous matrix. The tumor cells usually fail to experience their normal development into fat cells and remain in the

mucinous stage, but not always. The final proof of the origin from fat tissue is furnished by the observation of several cases collected over a period of years, in which typical myxosarcoma without a trace of fat was associated with typical cellular lipoma or liposarcoma (fig. 3).

ANATOMIC AND HISTOLOGIC CHARACTERISTICS OF FAT TISSUE IN THE SITES OF ELECTION OF MYXOSARCOMA

In a series of fresh cadavers and amputated limbs, dissections were made of the fat tissue about the knee, hip, elbow and shoulder in order to obtain any possible data that might bear on the origin of fatty tumors in these regions, which are the main sites of intermuscular myxosarcoma. The study did not prove very profitable. Abundant fat pads were found between the muscles, especially about the hip and Scarpa's triangle and in the buttocks. They filled the spaces between the muscles but were entirely free from the muscle investments and fasciae and from the subcutaneous layers of fat and were continuous with the periarticular masses of fat. They ensheathed arteries, veins and nerve trunks. In the upper part of the thigh there was a notable admixture of small nerve trunks coursing through the fat. The blood vessels were very abundant, especially large veins with muscular walls resembling sinusoids of the adrenals.

Microscopic sections threw no light on the origin of the tumors. Yet the deep fat pads contained many more small arterioles than are found ordinarily in depot fat. These tissues did not escape the inroads of the diseases from which the subjects died, such as arteriosclerosis, thrombosis, periarteritis, leukemic deposits, lymphocytic infiltrations and varicosities. No evidence of the effects of trauma was observed, but slight fibrosis and regression of fat were noted in emaciated elderly subjects. As an anatomic source of myxosarcoma in the regions studied the fat pads were entirely adequate, and no other source of origin could be suggested. No definite areas of brown fat were encountered except possibly about the knee joint. Deep lipoma lying between the muscles of the extremities was not infrequently observed.

CLINICAL ASPECTS

Intermuscular myxosarcoma occurs chiefly in middle-aged married women but also in males at nearly all ages after infancy. A history of trauma has not been noted in the present cases, but trauma is not infrequently alleged to precede true liposarcoma. The tumor begins as a painless swelling of the deep tissues and grows steadily but not rapidly, usually reaching a large bulk before demanding the attention of the patient (fig. 1). The tumor is firm but not as firm as ordinary

liposarcoma and not hard like neurosarcoma. Owing to the depth of the tumor, the whole limb may be uniformly swollen. Attempted excision of the tumor usually is partly successful owing to the encapsulation of the outlying lobules, but the deeper portions are difficult to reach and recurrence is nearly constant. The tumor then fungates through the operative scar and becomes infected and necrotic, and the patient dies from severe sepsis. The tendency for distant metastases to occur is less than in the case of most other types of cellular sarcoma.

The encapsulated multilobulated tumor lies between and, as a rule, does not invade the muscles, but recurrent growths breaking the capsule

Fig. 1.—Gross anatomy of an intermuscular myxosarcoma of the thigh.

may invade freely the muscles, the fat tissue and the skin. The texture is that of smooth elastic mucous tissue, moderately vascular and without much tendency to necrosis.

Section shows a peculiar and highly characteristic structure, composed of a fine network of capillaries or small arterioles and supporting mucous material in which are a few round or spindle cells, not very hyperchromatic. Fat cells are generally missing, but in the few cases mentioned there has been a considerable admixture of lipomatous tissue of the small cell embryonal type. The cells seem to be derived entirely from the adventitial or endothelial cells of the blood vessels. The process must therefore be interpreted as a capillary or arteriolar angioma, with excessive mucus or occasional production of fat. It reproduces the

process of the formation of fat in the embryo as described by Schaffer and others.

The common liposarcoma occurs in the same locations and presents much the same clinical features, but usually it is more rapid in course, firmer, more prone to yield pulmonary, cutaneous and general metastases and equally dangerous to life.

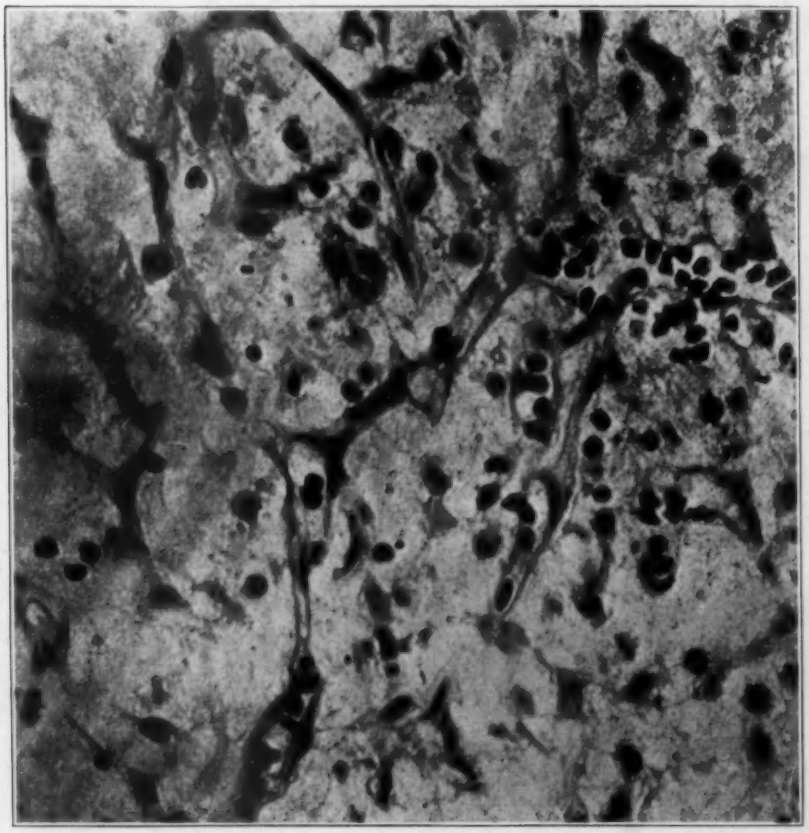

Fig. 2.—Detail of the structure of a myxosarcoma. All the proliferating cells seem to be derived from the walls of capillaries.

Yet the structure of the common liposarcoma is entirely different from that of myxosarcoma. It shows a diffuse growth of large or small polyhedral granular cells in which the proportion of fat globules diminishes with the grade of anaplasia. It presents a wide variety of structures, from diffuse, perithelial and alveolar sarcoma to very anaplastic, malignant, hyperchromatic, indifferent round cell sarcoma. Foci of fat cells are commonly found in some areas. Mucous degeneration may be present, but never to the extent seen in myxosarcoma. I

have not found combinations of granular cell liposarcoma and myxosarcoma. The two processes seem to be notably distinct.

On the basis of the data mentioned one may recognize the existence of two types of liposarcoma. One is composed of granular cells derived from adult fat cells, growing first within the cell membrane as in chronic inflammation of fat tissue and later becoming diffuse and appearing in many grades of anaplasia and malignancy, but not marked by any primary growth of blood vessels and not tending to produce mucous tissue. It represents the lawless phase of the growth of fat

Fig. 3.—Photomicrograph showing the structure of a myxoliposarcoma. Capillaries and mucous tissue are seen in one part and embryonal fat tissue in another.

cells observed in lesser degree in chronic inflammation of fat tissue. It may be called the adult form of liposarcoma (figs. 4, 5 and 6).

The other type of tumor follows the process of the embryonal growth of fat tissue and begins with the proliferation of capillaries and arterioles, the adventitial or endothelial cells of which, instead of going on to produce fat, yield chiefly mucus and occasionally embryonal fat tissue. This variety may be called embryonal liposarcoma or, on account of its anatomic relations, intermuscular myxoliposarcoma.

TREATMENT

The almost uniformly fatal outcome of liposarcoma and myxosarcoma of the extremities presents a melancholy picture and raises the question whether a more accurate recognition of the nature of

Fig. 4.—Photomicrograph showing an early stage of myxosarcoma from an outlying focus of a tumor about the knee joint.

these tumors and their unfavorable clinical course and the use of nonsurgical methods may not give better results. The decision in this question is a matter for cautious clinical judgment and experience. However, it may be stated that many forms of liposarcoma and of

myxosarcoma are radiosensitive, sometimes extremely sensitive. The structure of myxosarcoma with its fine capillary blood vessels suggests the source of the high radiosensitivity which has sometimes been exhibited by this tumor. The blood supply of primary liposarcoma and myxosarcoma seems to be delicately balanced and easily affected by high voltage irradiation. On recurrence neither of the tumors, how-

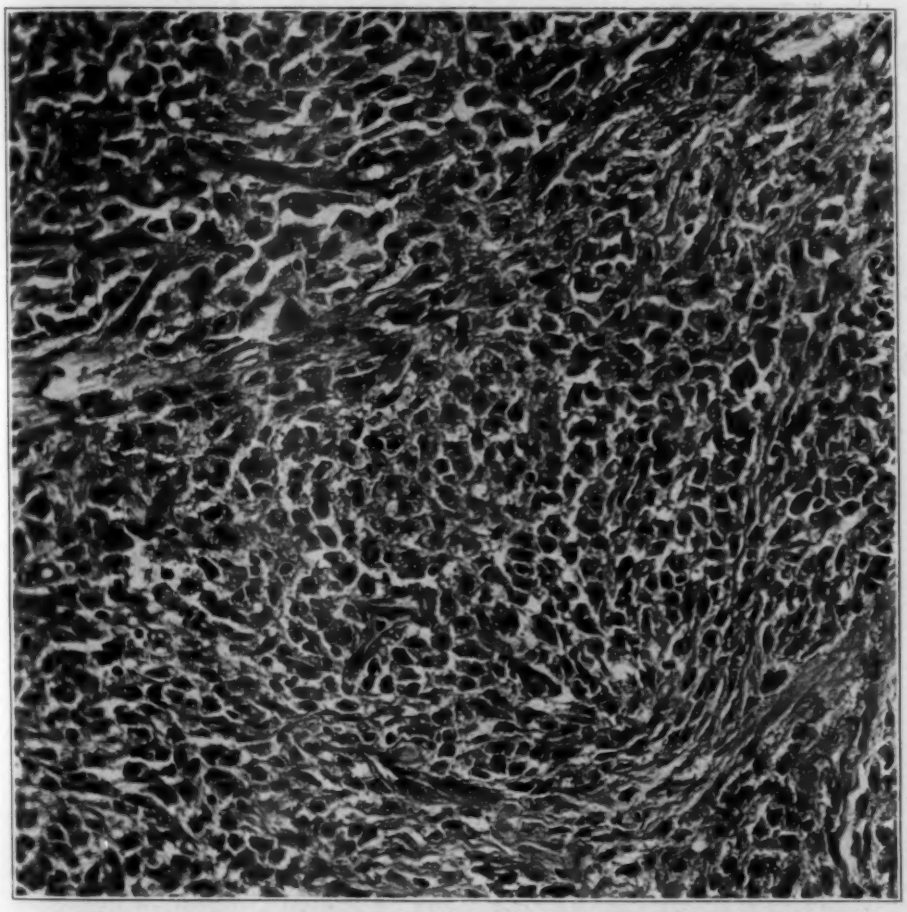

Fig. 5.—Photomicrograph showing the structure of an adult liposarcoma. Note the opaque granular cells. Many fat granules were demonstrated by sudan III.

ever, shows the same radiosensitivity, probably for the reason that the blood supply of the recurrent tumor is obtained from peripheral sources and not from one central system, since the tissue of the recurrent tumor on being released from any capsule grows diffusely.

I was sharply impressed by this fact in a case of a tumor in the early stage which was observed in 1915:

The patient was a middle-aged woman who on presenting herself at the Memorial Hospital had a bulky tumor of the false pelvis and another bulky tumor of the thigh, which had recurred after operation. The structure was that of a myxosarcoma. The larger tumor of the pelvis disappeared rapidly under irradiation with the old Müller x-ray tube, which delivered about 125 kilovolts. The tumor on the thigh resisted similar treatment completely and fungated through the scar; it became infected, and the the patient died as a result of sepsis. At autopsy the remains of the pelvic tumor were found as a flat mass of fibrous tissue covering the iliopsoas muscle.

Since most other forms of deep sarcoma of the limbs and of neurosarcoma, myosarcoma and osteogenic sarcoma recur after operation, and

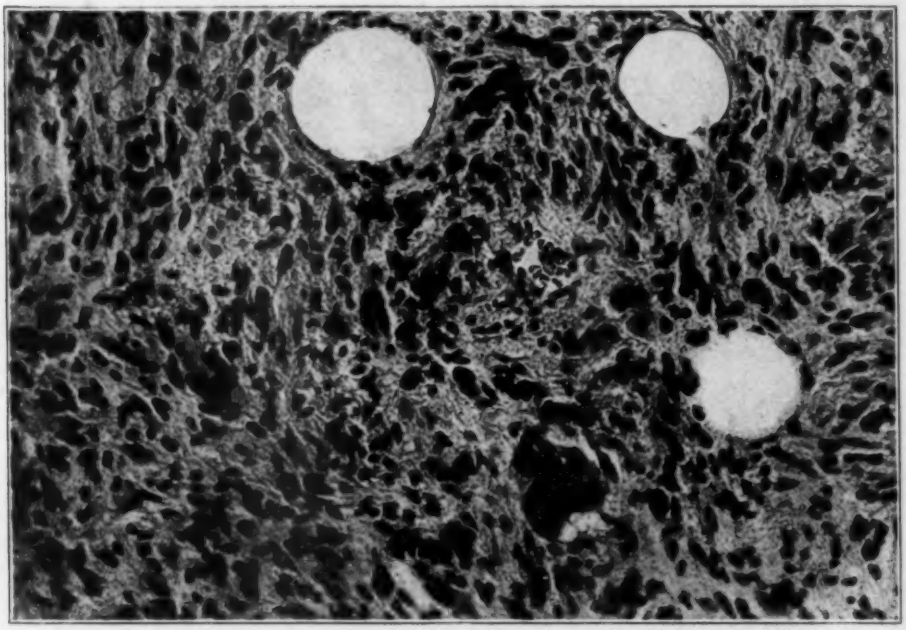

Fig. 6.—Photomicrograph of a highly malignant adult liposarsoma.

since some are radiosensitive, I venture to suggest that the primary treatment of all bulky deep sarcomas of the extremities, especially those of the thighs, arms and axillae, should be by irradiation, external or interstitial or both. With this policy some of the radiosensitive tumors might be controlled or cured. Others would doubtless resist, but the results could hardly be worse than those secured under the present surgical mode of attack.

ETIOLOGY

No special exciting factors can be discerned in the clinical histories of most of the patients with intermuscular myxosarcoma. The great majority of the tumors arise without any clinical indication of extraneous

factors. The occurrence in the same situation of lipoma, neurofibroma and mixed neurolipoma indicates that the incitement to growth must be spontaneous in the sense that the growth of all lipomas and neurofibromas is spontaneous or dependent on ill defined abnormalities in structure or nutrition of the affected region. The occurrence of many chronic lesions in the fat pads of the thigh as part of the manifestations of general diseases of the body has already been mentioned.

A history of trauma has frequently been given by patients presenting intermuscular sarcoma, but the importance of trauma must be accepted with caution, since the majority of patients give no hint of any trauma.

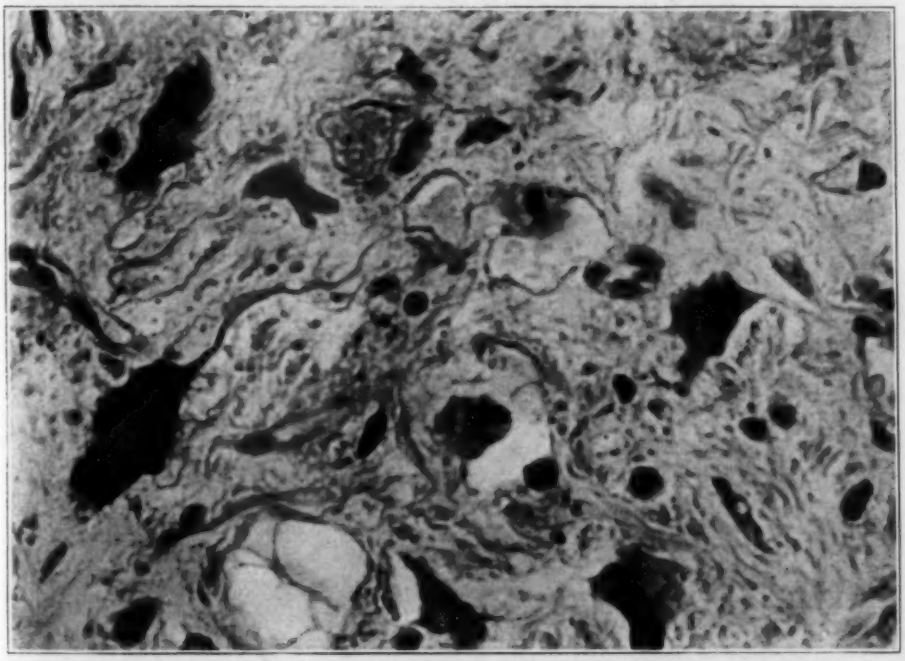

Fig. 7.—Photomicrograph of a degenerating fibrosing but malignant adult liposarcoma.

A history of trauma is a most definite and reasonable explanation for the origin of tumors of the subcutaneous fat tissue and of the adult form of liposarcoma rather than of the embryonal type.

In the following case a traumatic origin seems to be reasonably well established for a low grade liposarcoma:

A highly intelligent middle-aged woman stated that she was in the habit of striking her right thigh against a projecting corner of a bureau in passing from one room to another in her apartment. After many such mild bruises she noticed a persistent tender swelling in the subcutaneous tissue, which slowly increased for several months. The mass was then excised. The material removed was a mass

of subcutaneous fat tissue, 3 by 4 cm. in diameter, the central portions of which were opaque, soft and cellular. On section, the opaque portions consisted of a diffuse growth of adult fat cells, with granular cytoplasm, hyperchromatic nuclei and the general structure of a beginning liposarcoma of moderate but definite malignancy. There was no recurrence.

Reviewing a series of histories of cases of liposarcoma of the adult type, I have been somewhat impressed by the frequency with which a definite history of severe trauma with resulting hemorrhage has preceded the appearance of the tumor at the point of injury. Since traumatism to fat tissue is often followed by marked proliferation of fat cells and progressive productive inflammation, it is not unreasonable to assume that under special circumstances the proliferation may take on a malignant character, especially in the subcutaneous layers of fat. That similar trauma can affect the deep fat pads of the thigh is much less acceptable. On the other hand, it is clear that these deep fat tissues are much exposed to chronic trauma by stretching, straining and muscular compression, to which, rather than to any single trauma, the incitement to growth might be referred.

SUMMARY

The term fascial sarcoma should be restricted to the fibromas, fibrosarcomas, fibrochondromas or parosteal osteosarcomas originally described and designated as fascial sarcoma by Virchow. It should not be employed for intermuscular myxosarcomas.

The intermuscular myxosarcoma, often called fascial sarcoma, is probably derived from fat lobules and presents the structure of embryonal mucous tissue or embryonal fat tissue. It is rarely, if ever, of traumatic origin and is often radiosensitive.

The common liposarcoma of the trunk and limbs is derived from adult fat tissue and presents the structure of large granular cells such as those seen in chronic inflammation of fat tissue. The structure varies greatly with the degree of malignancy. It seems to be occasionally of traumatic origin. The degree of radiosensitivity of the primary tumor is uncertain, but the recurrent tumors are radioresistant.

It appears that two types of liposarcoma may be recognized, one the myxoliposarcoma of embryonal structure and the other the granular cell liposarcoma of the adult type.

Liposarcoma of both types is comparatively common in the region of the hip, knee, shoulder and trunk. It runs a characteristic clinical course, usually recurring after operation and proving fatal from infection, sepsis and metastases to the lungs. Since some are radiosensitive, it is recommended that all bulky tumors of the soft parts be submitted to treatment with high voltage irradiation before resort to surgical intervention.

ANAL DUCTS

COMPARATIVE AND DEVELOPMENTAL HISTOLOGY

CLAUDE C. TUCKER, M.D.
AND
C. ALEXANDER HELLWIG, M.D.
WICHITA, KAN.

The large rôle in anal disease which is played by the crypts of Morgagni is generally recognized. According to Rankin, Bargen and Buie,[1] infection of these structures is the underlying factor not only of cryptitis, anal fissure, periproctitic abscess and anal fistula but also of hemorrhoids. Our own microscopic studies [2] of more than four hundred proctologic specimens demonstrated that the crypts of Morgagni were not by themselves responsible for the frequency of anal infection but that infection originated as a rule in preformed tubules which we called anal ducts. They were found to open into the crypts, affording a ready path for infective organisms from the intestinal lumen into the wall of the anal canal.

While the pathogenic significance of the anal ducts was thus established, the question presented itself whether these structures have a definite function or whether they represent a vestigial organ. We hoped to obtain some information regarding the nature of the anal ducts by studying embryonic and comparative anatomic material. The present paper is based on histologic studies of the anal region in the dog, cat, guinea-pig, rabbit and chicken and of longitudinal sections of six human embryos.

In textbooks the anatomic fact is not sufficiently stressed that the rectal mucosa with its Lieberkühn crypts does not join directly with the epidermis of the anal canal but that a circular zone, varying in height from 0.5 to 1.2 cm., separates the entodermal and the ectodermal portion. Its epithelium is composed of several layers of polygonal cells, while the superficial cells are columnar. It is only from this transitional epithelium of the intermediate zone that we have found the anal ducts to originate and extend into the submucous or muscular layers of the anal canal (figs. 1 and 2).

From the Department of Surgery and Pathology, St. Francis Hospital.

1. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: The Colon, Rectum and Anus, Philadelphia, W. B. Saunders Company, 1932.

2. Tucker, C. C., and Hellwig, C. A.: Histopathology of Anal Crypts, Surg., Gynec. & Obst. **58**:145, 1934.

The histologist who receives a small section from the intermediate zone of the anal canal without knowing the exact source will hesitate to diagnose it as part of the intestines; rather he will take it to be a section of the urethra with para-urethral ducts. So striking is the resemblance between the intermediate zone of the anal canal and the derivatives of the urogenital sinus that a developmental relationship between these two structures seems obvious.

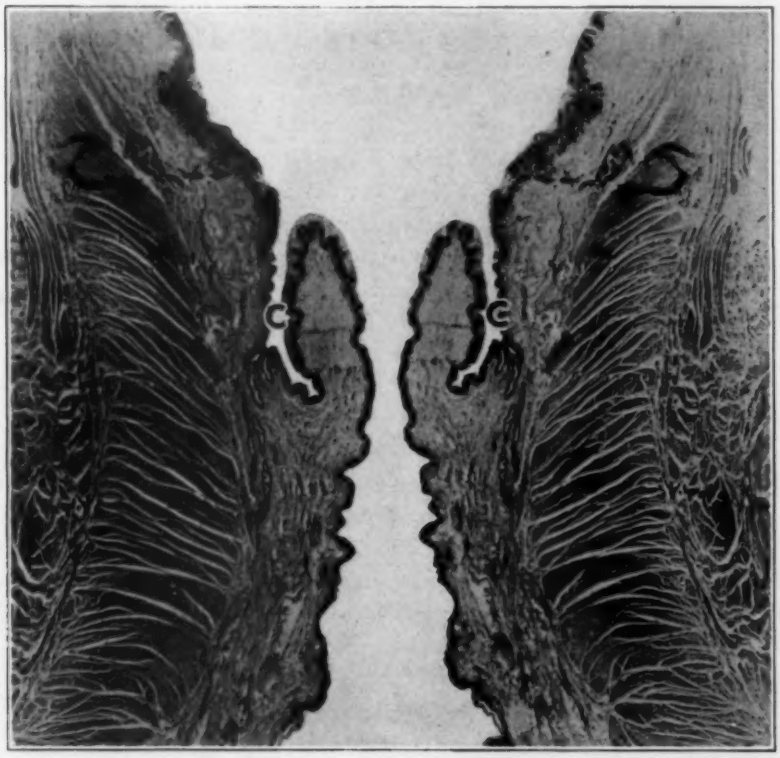

Fig. 1.—A longitudinal section through the anal canal in man. The intermediate zone (*C*) is between the entodermal and the ectodermal portion. The anal ducts, opening into *C*, are well developed. (Microscopic section by courtesy of J. E. Pritchard, Montreal, Canada.)

We examined, first, the anal region of several animals. Of the mammals, the rabbit (fig. 3), the dog and the pig have in the intermediate zone complex glandular organs which seem to have a definite, probably sexual, function by producing odoriferous substances. Still more interesting were our observations in fowls. The wall of the cloaca in the chicken is surrounded by a voluminous gland. During the first year of life, this glandular organ is embedded in dense lymphoid

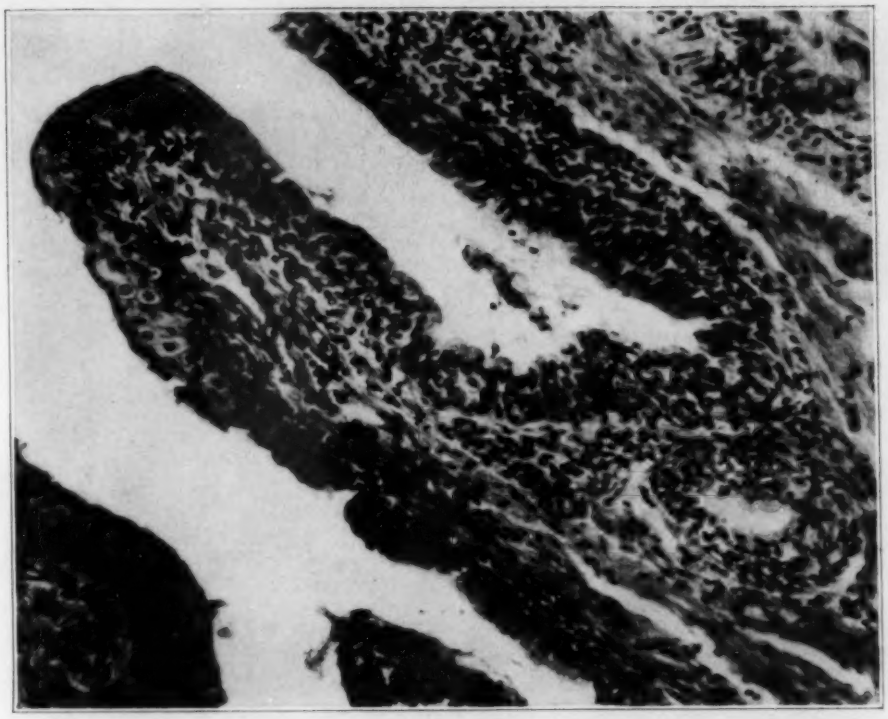

Fig. 2.—A section showing a branching of the anal duct. The epithelium is transitional and stratified columnar.

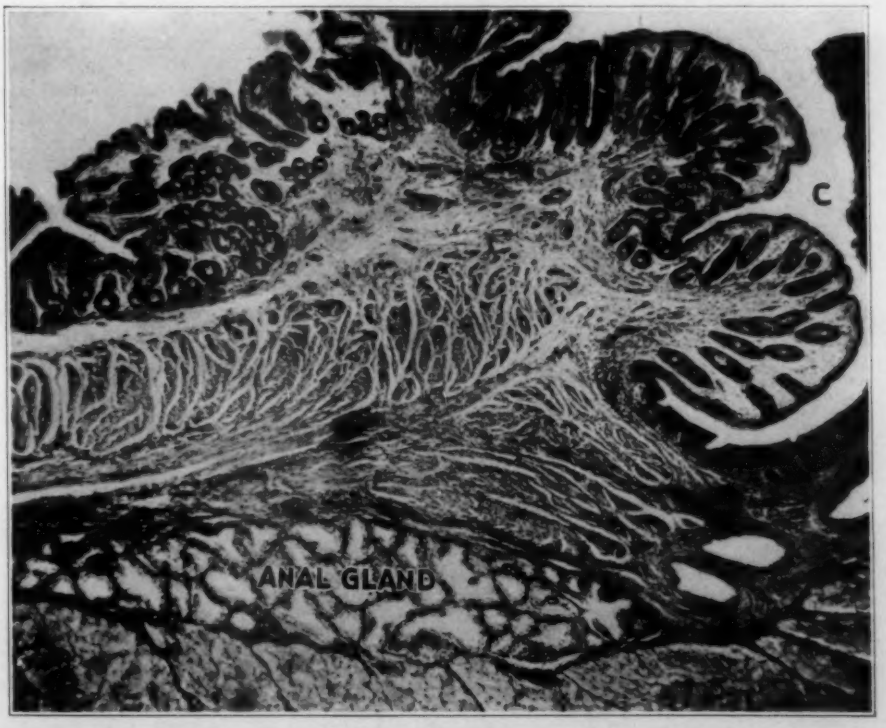

Fig. 3.—A large anal gland in a rabbit which seems to have a sexual function. The mucin stain gave negative results. The excretory duct opens into the intermediate zone of the anal canal (*C*).

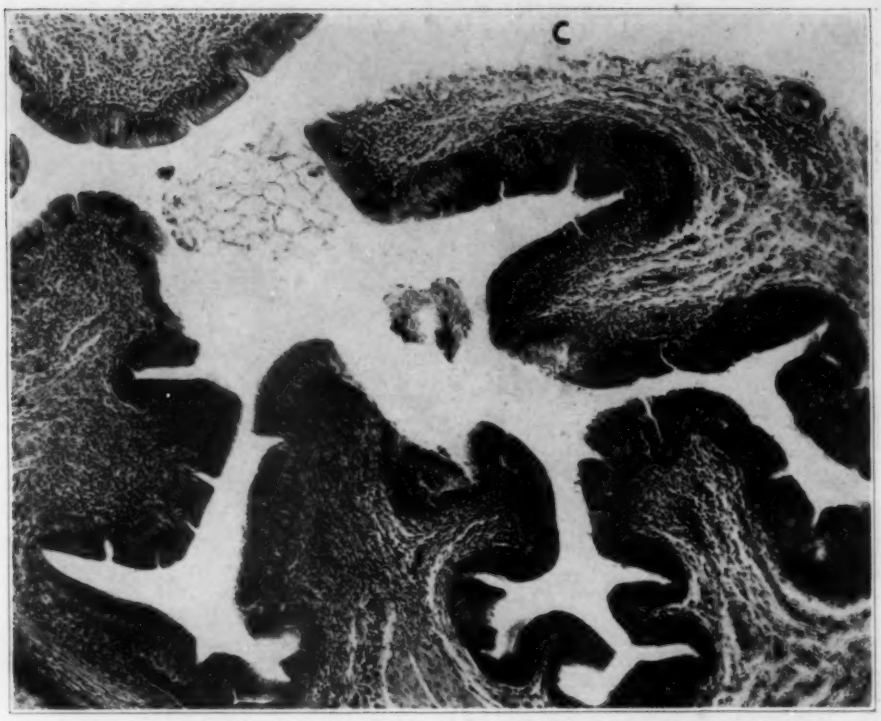

Fig. 4.—The cloacal gland of a chicken. It is homologous to the prostate, para-urethral and anal glands of higher animals.

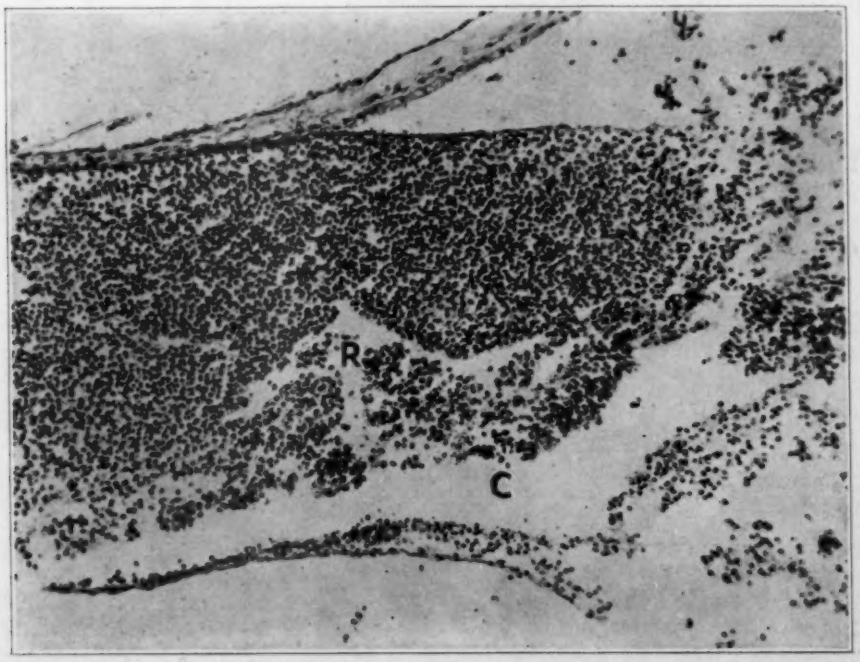

Fig. 5.—A longitudinal section through a human embryo 0.5 cm. long. The fetal cloaca (*C*) is connected with the lower end of the rectum (*R*) and is closed off from the outside by the cloacal membrane.

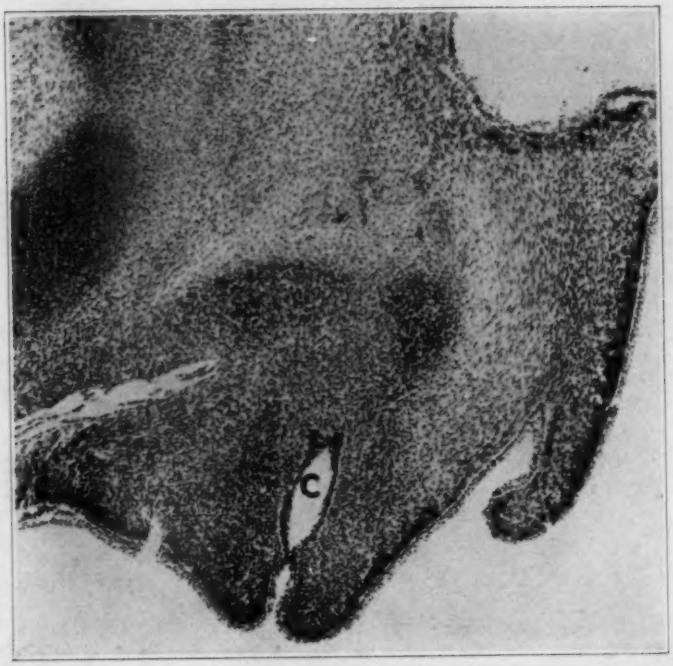

Fig. 6.—A longitudinal section through a human embryo 18 mm. long. The cloaca has become divided into the urogenital sinus and the intermediate zone of the anal canal (*C*). The anal membrane, which is a remnant of the fetal cloacal membrane, is still intact.

Fig. 7.—A section through the anal region of a human embryo 32 mm. long. Three well formed anal ducts are developing from the transitional epithelium of the intermediate zone (*C*).

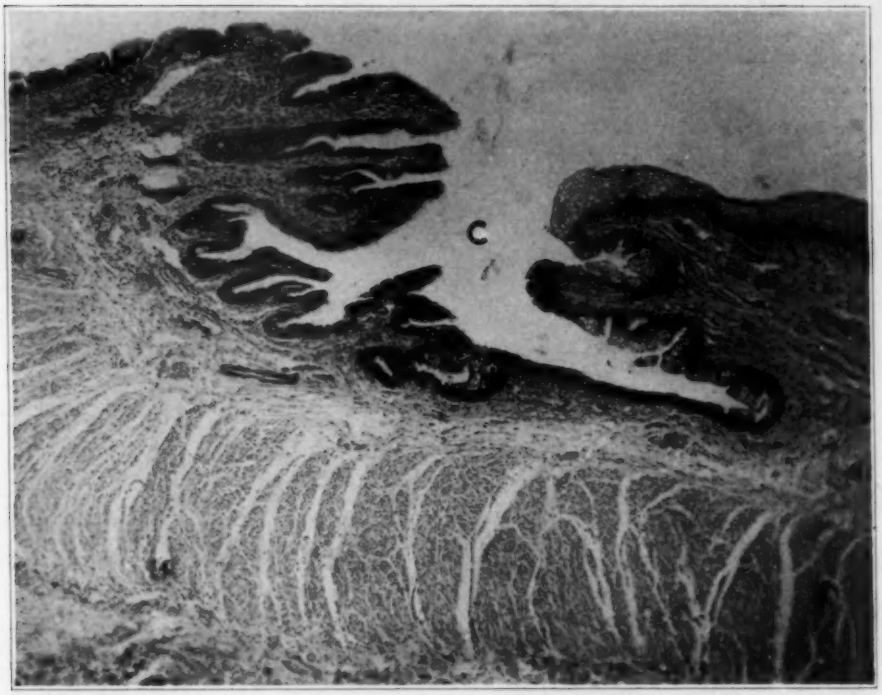

Fig. 8.—The anal canal of a new-born infant. *C* indicates the derivative of the fetal cloaca. Several well formed ducts open into the intermediate zone.

Fig. 9.—An infected anal duct disclosed during an operation for anal fistula. The fistula originated from this duct. The upper forceps is held in the same direction as the infected duct.

tissue. Our own studies failed to elucidate the function of this large cloacal gland, nor does the newest monograph on the anatomy of Gallus domesticus [3] contain any pertinent data. The fact, however, that this gland has been called the anal, prostate or Cowper's gland by zoologists indicates that the anal, prostate and para-urethral glands of mammals are homologous to this cloacal gland in the fowl (fig. 4).

The development of anal ducts was studied in six human embryos of different age. The youngest was 0.5 cm. long, which would cor-

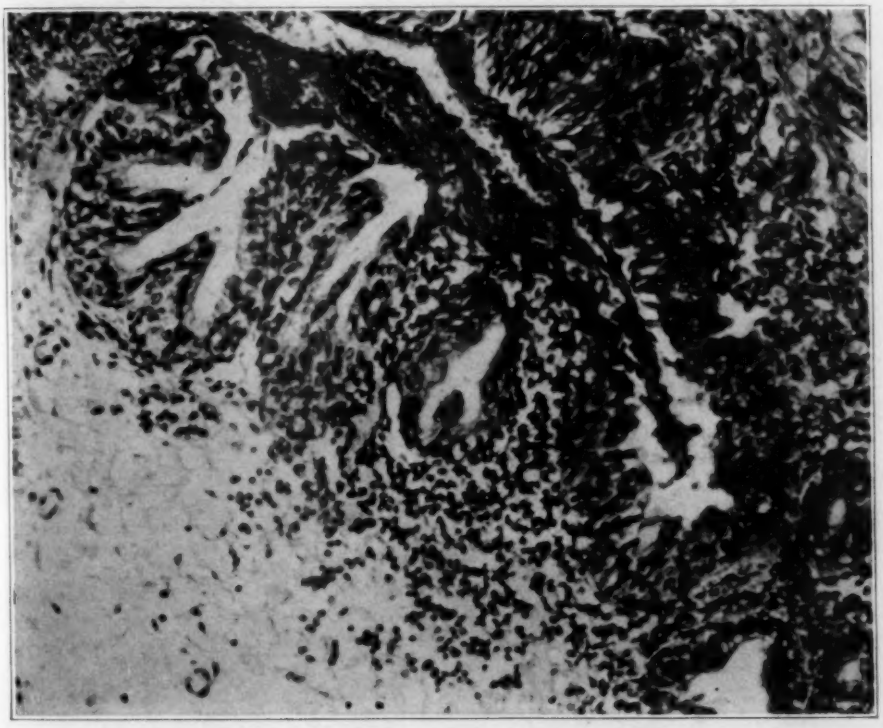

Fig. 10.—An infected anal duct with leukocytes in the lumen and in the wall. The epithelium is preserved in many areas.

respond to an age of 3 weeks. The work of Johnson [4] was confirmed. The rectum in the earliest stage presented at its lower extremity a spindle-shaped swelling which extended into the fetal cloaca. The cloaca was closed off from the outside by the cloacal membrane (fig. 5). The division of the cloaca into the urogenital sinus and the

3. Calhoun, M. L.: The Microscopic Anatomy of the Digestive Tract of Gallus Domesticus, Iowa State College J. Sc. **7**:261, 1933.

4. Johnson, F. P.: The Development of the Rectum in the Human Embryo, Am. J. Anat. **16**:1, 1914.

rectum takes place in embryos about 15 mm. long. When the cloaca becomes divided into dorsal and ventral parts the dorsal half of the fetal cloaca becomes incorporated with the rectum and forms the intermediate zone of the anal canal (fig. 6). In embryos about 30 mm. long we found distinct anal ducts arising from the upper portion of the zona intermedia (fig. 7). All were distinctly tubular and gave off several branches at various levels. The glandular ducts extended sometimes through the internal sphincter and terminated in the connective tissue between the muscle layers. The epithelium of these ducts was stratified

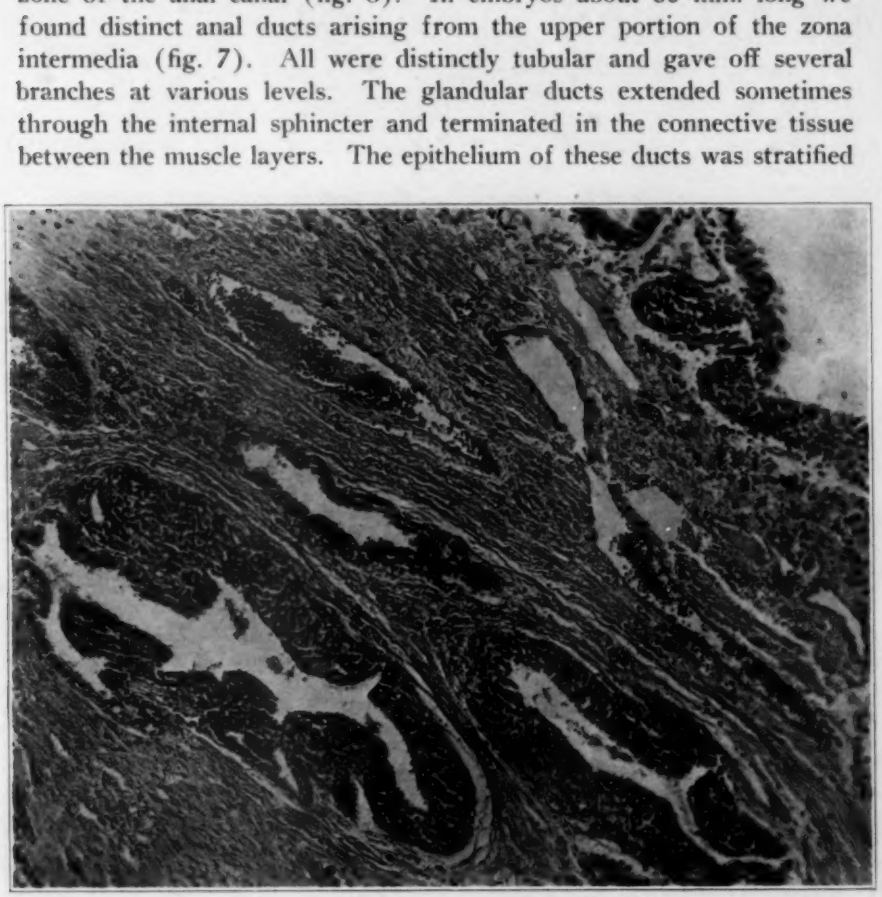

Fig. 11.—Infected prostatic ducts with leukocytes in the lumen and within the transitional epithelium of the wall.

and columnar and, in the branches, became cuboidal (fig. 8). In our human material the development of the anal ducts took place at the same time as did that of the prostate and the para-urethral ducts. The latter originate from the urogenital sinus, a derivative of the anterior portion of the cloaca.

Our conception that the intermediate zone of the anal canal and the urethra are derivatives of the same fetal organ, namely, the cloaca, and that the anal, prostate and para-urethral ducts are homologous structures was further substantiated by pathologic observations. Figures 9, 10,

11 and 12 show a striking resemblance between infected anal prostate and para-urethral ducts. All three structures are often involved in gonorrheal infection. Martin [5] pointed out recently that in gonorrheal infection of women the anal canal also becomes infected in about half the cases. In our own series of cases of infected anal ducts, 22.1 per cent were caused by the gonococcus. The transitional epithelium of the intermediate zone of the anal canal, with its anal ducts, apparently furnishes the same favorable biologic conditions for the Neisser coccus as do the other derivatives of the cloaca. And the same rôle which in

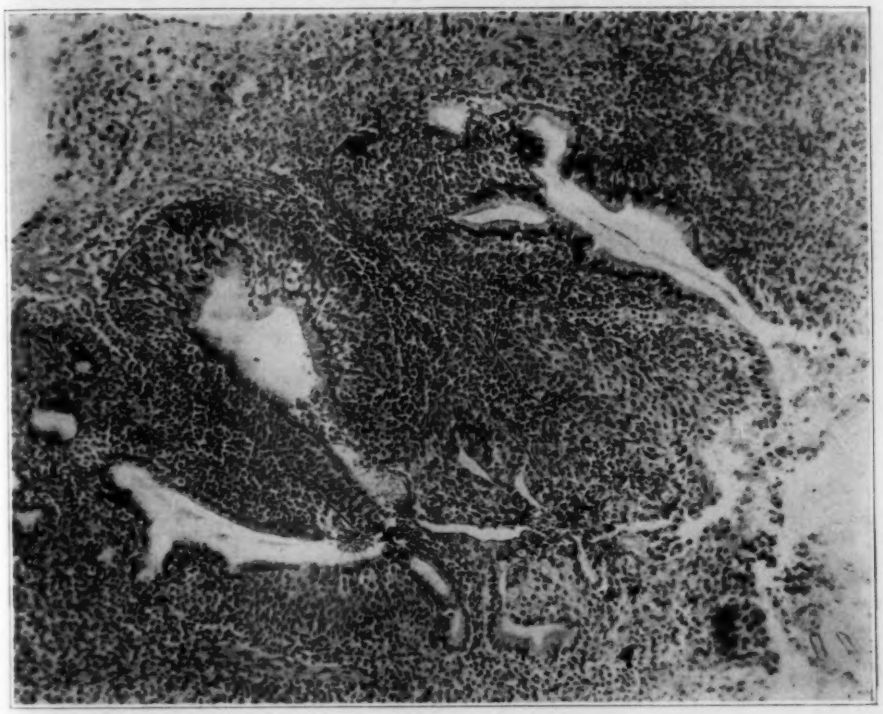

Fig. 12.—Infected para-urethral ducts with leukocytes and plasma cells in the wall and surrounding the ducts. Gynecologists call this condition urethral caruncle.

reinfection is played by the prostate and para-urethral ducts by harboring the gonococcus is played by the anal ducts.

CONCLUSIONS AND SUMMARY

Anal ducts are preformed tubular structures which open into the crypts of Morgagni. Infection of these ducts is responsible for so-called cryptitis, anal fistula and periproctitic abscess.

5. Martin, C. L.: Rectal Contamination in Women, J. A. M. A. **104**:192 (Jan. 19) 1935.

In human embryos the anal ducts develop at the same time as the prostate and para-urethral ducts. The intermediate zone of the anal canal and the urogenital sinus are derivatives of the same fetal organ, i. e., the cloaca.

In the chicken a large cloacal gland is found which resembles the prostate, para-urethral and anal ducts of higher animals. The rabbit, dog and pig have complex glandular organs in the intermediate zone of the anal canal which seems to have a sexual function.

The anal ducts in man are vestigial remnants of these large glands.

From a pathologic point of view, the anal ducts have much in common with the prostate and para-urethral ducts. All three play an important rôle in gonorrheal reinfection by harboring the gonococcus.

FIBROSARCOMA OF THE RIGHT FOREARM WITH EXTENSIVE GROWTH INTO THE CEPHALIC VEIN

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The following case is reported on account of the rarity of sarcoma, especially fibrosarcoma, in the veins occurring as an extension of sarcoma in their vicinity and not as true metastasis.

REPORT OF A CASE

History.—A. S., a man aged 42 years, married, with four living children, was apparently in good physical condition except for a tumorous lesion extending from the right wrist to the forearm (fig. 1). This lesion was first observed about eight years before examination, and started as a small lump near the palmar surface of the wrist; there were no symptoms of pain or any inflammation. The swelling gradually and slowly increased until about one and one-half years before examination, when it was observed to be spreading up the forearm; it finally extended from the wrist to the biceps. On examination it was seen that on the flexor surface and radial side of the right forearm there was a superficial swelling with two red areas. The original site of the swelling at the wrist became reddened about four years before examination, and there was another reddened area higher up on the forearm.

The patient's history was irrelevant. He had the usual diseases of childhood and had gonorrhea and syphilis. The abdomen and other areas were normal. There was no history of traumatism.

Examination.—The tumor appeared very vascular with some telangiectatic areas on the older nodule. There were two distinct nodules. The smaller, older, movable nodule was located over the right wrist joint and extended into the palm and about one-third the distance up the forearm; on its surface there were two or three distinctly hyperemic areas. The main mass was firm, hard and rounded, and there were seven small radiating nodules which could be felt extending from the surface. The second main nodule was of more recent origin, freely movable and compressive; it did not appear to be so vascular as the first and was less firm. A longitudinal tail-like extension spread along into the flexor surface of the arm (fig. 2). No other swollen areas were found in the vicinity or elsewhere, nor was there any suggestion of such. The lymph glands of the axilla were not enlarged.

From the clinical data it seemed that the condition was of the nature of a progressive, fibrous or cartilaginous process of the subcutaneous tissue process of a benign character.

The roentgenologist reported a large, soft tumor of the right forearm, which appeared to be of lymphatic origin, with an irregular linear type of calcification in the lower part of the mass; there was no involvement of either the radius or the ulna (fig. 3).

Read before the Western Surgical Society, St. Louis, Dec. 7, 1934.

Fig. 1.—The appearance of the growth on the volar surface of the forearm.

Fig. 2.—The extension of the growth on the radial side of the forearm with extension upward within the cephalic vein.

Fig. 3.—Roentgenogram of the forearm showing the two masses, one at the wrist and the other higher up on the forearm. In the lower mass especially are seen areas of calcification which most probably resulted from hemorrhages into the tumor.

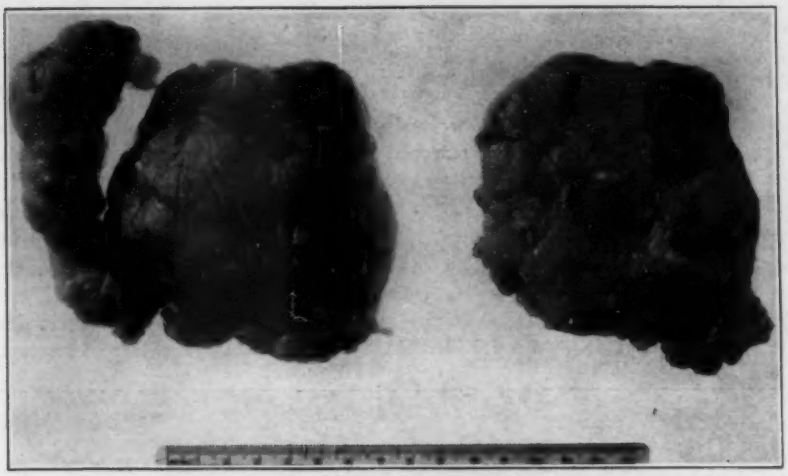

Fig. 4.—The lower mass, near the wrist.

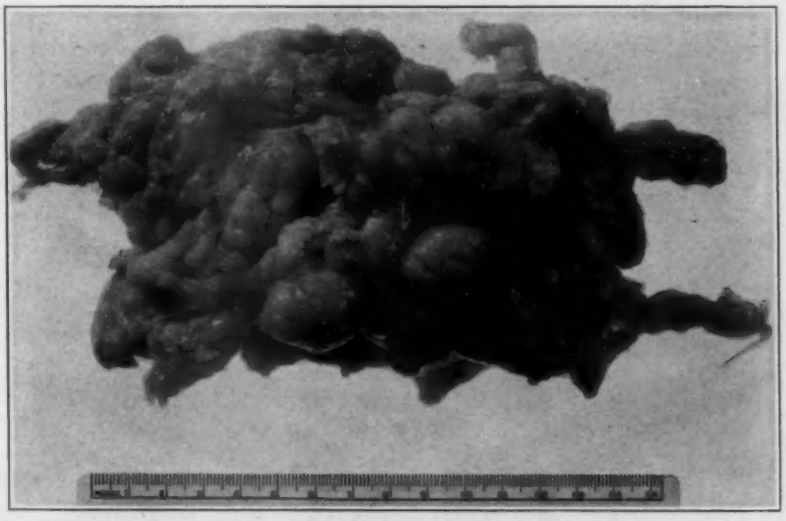

Fig. 5.—The upper mass, near the elbow joint.

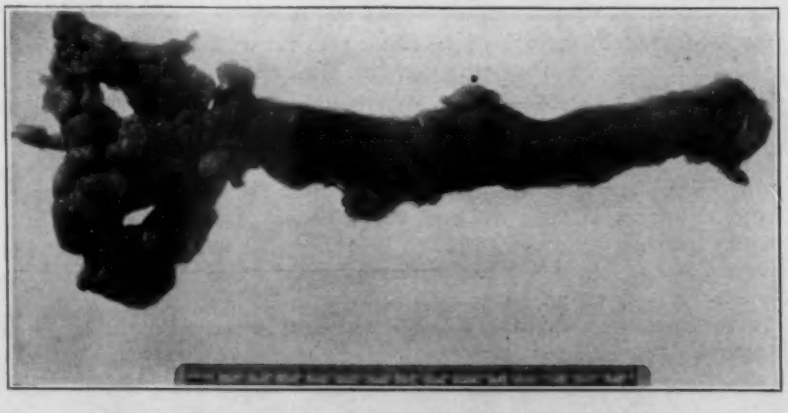

Fig. 6.—The tumor extending upward in the cephalic vein.

No definite diagnosis could be arrived at from the evidence at hand, and it was determined to make a biopsy on material from the original part of the growth; removal of this material caused profuse hemorrhage. It was then decided to excise the masses with the patient under gas anesthesia.

Operation.—The tumor was found to be an invasion of the blood vessels (veins) of the forearm, dilating them considerably, especially the median cephalic vein. The growth had invaded or replaced some of the muscle tissue, especially the palmaris longus muscle, but it had not involved the bones. The mass consisted of large nodules which were friable. In the distal part there were some areas

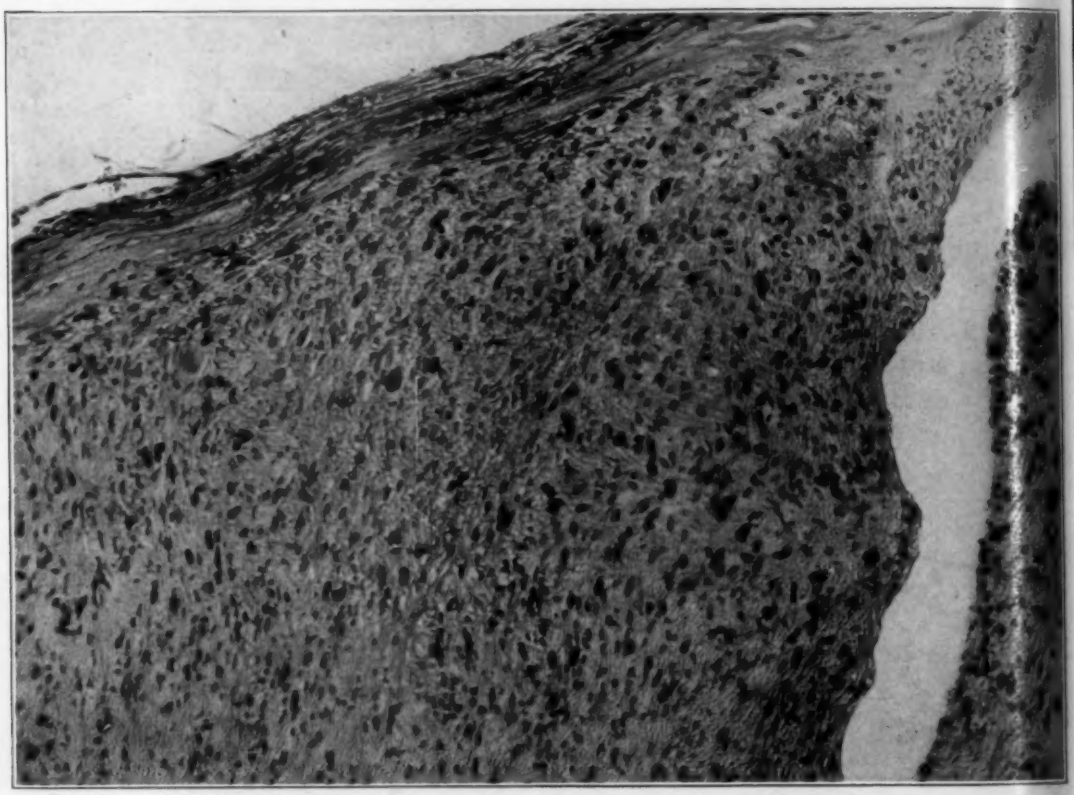

Fig. 7.—A photomicrograph of the tumor with the wall of the vein at the top. A typical intratumor blood vessel is seen near the right edge. The large amount of fibrils and fibers is evident from the distance between the fibroblastic tumor cells.

of calcification. The mass was dissected away from the surrounding tissues, and with careful hemostasis there was very little bleeding. Following removal of the constrictor muscle no pulsation could be felt in the radial artery, and the hand and arm were cold and lifeless. It was therefore decided to amputate the lower third of the arm 7 cm. above the elbow, which was accordingly done.

The two tumors were 7 and 9 cm. in diameter, respectively; the larger one was embedded in muscle and fascia, and surfaces made by cutting were uniformly

gray except for the heavier stroma coursing here and there so as to produce a trabeculated appearance. The extremity from which the tumor had been excised on being dissected showed extensive invasion by masses of similar tumor tissue which apparently were intimately related to the peripheral nerves.

Histologic Examination (by Dr. E. R. LeCount).—The growth belonged to the group of fibrosarcomas for which the old term desmoid is still occasionally employed, growths more commonly encountered in the broad ligaments of women and in the subcutaneous tissues of the trunk or sides of the neck. They are rare in the back wall of the trunk but occur frequently in the lower half of the

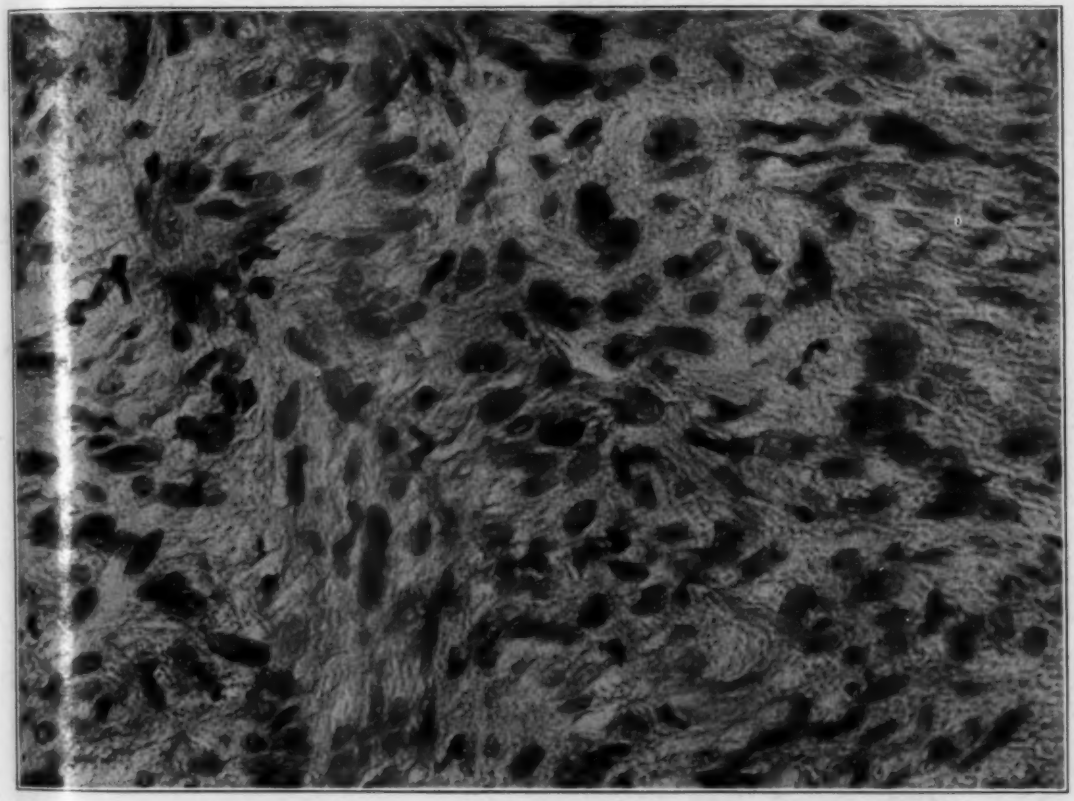

Fig. 8.—A photomicrograph showing the relative amount of the tumor tissue occupied by fibers and by the cells from which they arose. On the right and near the top are a few masses of aggregated nuclei resembling giant cells.

abdominal wall. They are much less malignant than fascial fibrosarcomas of, for example, the thighs. Occasionally they recur after removal and then usually grow more rapidly.

As a rule, they have a thin capsule and grow in an expansile fashion. One removed several years ago by Dr. Kellogg Speed[1] grew in the upper part of the abdominal wall on the right side and passed through its capsule to invade the

1. Speed, Kellogg: Tumor of Chest Wall, S. Clin. North America **10**:213 (April) 1930.

abdominal cavity, liver and diaphragm just below the costal arch but produced no secondary metastatic growths. When these tumors give rise to secondary regional or distant separate metastatic growths it is after the sarcomatous element has become more dominant in new tumors which appear after the primary ones are removed.

The nuclei of the tumor cells were far apart (fig. 8), and the intervening tissue was full of fibers which stained blue with aniline blue and both blue and yellowish with phosphotungstic acid and hematoxylin. All the stages of development of fibrils, reticulum and the heavier collagen bands were readily followed in sections of high magnification in preparations suitably stained.

In many places the nuclear material was in masses so that multinucleated cells were simulated, but without any uniform pattern. The blood vessels all had thin walls (fig. 7), and there was nothing left of the wall of the vein surrounding so much of the growth (fig. 7) to indicate its character. In some sections there were small edematous regions.

From the foregoing observations there appears to be no doubt that the tumor was a fibrosarcoma of the veins of the forearm.

COMMENT

Tumors of the veins are fairly rare. They may be primary or secondary, benign or malignant. Independent sarcomatous masses in the veins, whether primary or secondary, are very rare, and textbooks such as those of Ewing,[2] Ribbert,[3] Bland-Sutton[4] and Borst[5] give little attention to them; Nothnagel, in his "Specielle Pathologie,"[6] mentioned them especially as secondary carcinoma.

Among the reports of benign tumors invading veins, Aufrecht[7] in 1860 reported a case of primary myoma of the right saphenous vein originating in the region of the internal malleolus. The intima and adventitia of the vein were normal. Boettcher[8] in 1869 reported a case of a similar lesion in the ulnar vein except that all three coats of the vessel were involved. Schnijder[9] reported a case of myoma of the marginalis lateralis pedis. Cornil[10] in 1896 observed at autopsy

2. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

3. Ribbert, M. W.: Geschwulstlehre für Aerzte und Studierende, Bonn, F. Cohen, 1904, p. 258.

4. Bland-Sutton, J.: Tumors Innocent and Malignant, London, Cassell & Co., Ltd. 1917.

5. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902.

6. Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Holder, 1900, vol. 15, pt. 3, p. 540.

7. Aufrecht: Ein Myom der Vena Saphena, Virchows Arch. f. path. Anat. **44**:133, 1868.

8. Boettcher: Myom einer vena ulnaris, Virchows Arch. f. path. Anat. **47**:372, 1869.

9. Schnijder: Centralbl. f. allg. Path. u. path. Anat. **25**:529, 1914.

10. Cornil: Myomes dans les veines du bras, Bull. Soc. anat. de Paris **10**:725, 1896.

myomas with smooth fibers developed at the expense of the vascular walls of the veins of the arm. There was a myoma of the vena brachialis the size of a fist in which the muscular coat of the wall of the vein was completely involved. Cornil's report is only a short anatomic note on the autopsy.

Breus [11] reported a case of secondary myxoma of the vena cava ascendens and the heart. The original tumor was in the testicle whence the tumor cells spread through the plexus spermaticus. The venous tumor was not adherent to the vascular walls. Cernezzi [12] also reported a case of myoma of the plexus spermaticus.

Cartilaginous benign tumors which invade blood vessels are not infrequent. Virchow,[13] in his work on tumors, included a report of an enchondroma originating in the fibula. There are some others reported in the literature, originating especially in the pelvic bones, as in the case of Pfeiffer.[14] These tumors generally degenerate into a malignant process; this will be referred to later.

I am unable to find a report of any other than the case of Langenbeck of a benign fibroid, but degeneration of the veins themselves occurs fairly frequently. As far back as 1860 Langenbeck [15] reported a case of a fibroid originating in the periosteum of the clavicle, which came to resection. The common jugular and also the subclavian vein were involved by extension of the tumor, and the internal jugular vein was thrombosed.

There are many cases reported in the literature of carcinoma forming primary, but more usually secondary, masses by direct extension within veins. In a recent issue of *The Journal of the American Medical Association,* Holt [16] reported the extension of a primary adenocarcinoma of the thyroid gland into the superior vena cava which was continued into the right auricular chamber and into the innominate, right subclavian, internal jugular and thyroid veins as well as downward into the inferior vena cava. Regarding malignant tumors, in this report I am, however, more directly concerned with sarcoma. Although dissemination of metastatic sarcoma by the venous route is common enough, actual vascular sarcomatous tumors within the veins by extension are rare. Sarcoma or more probably endothelioma may be a primary tumor,

11. Breus: Ueber einem innerhalb des Venensystems bis in das Herz gewucherten Hodentumor, Wien. med. Wchnschr. **28**:767, 1878.

12. Cernezzi: München. med. Wchnschr. **58**:676, 1904; cited by Van Ree.[24]

13. Virchow, R.: Virchows Arch. f. path. Anat. **8**:404, 1855.

14. Pfeiffer, F.: Beitrag zur Lehre von dem Enchondrom des Beckens, Erlangen, F. Junge, 1890.

15. Langenbeck: Beiträge zur chirurgischen Pathologie der Venen, Arch. f. klin. Chir. **1**:1, 1861.

16. Holt, W. L.: Extension of Malignant Tumor of Thyroid into Great Saphenous Vein and Right Heart, J. A. M. A. **102**:1921 (June 9) 1934.

and Ribbert remarked that sarcoma of the vessels is usually primary and arises from the muscular wall, though not in all cases. According to Borst, an angiosarcoma may be of vascular origin, the tumor cells entering the vessel from without. Nothnagel, in his monumental work, referred to intravascular benign and malignant tumors.

Langenbeck [15] in 1861 reported a case of sarcoma which was primary in the parotid gland but which after several years extended to the internal jugular vein. In the same report he mentioned a case of sarcoma of the sheaths of the axillary vessels by extension from tissue in the vicinity of the pectoralis major and coracobrachialis muscles. He did not say if there were any masses of tumor cells within the lumens of the vessels.

Sarcoma of the wall of the aorta has been reported by Auffermann [17] and Miura.[18]

In Schrotter's [19] case a lymphosarcoma of the anterior mediastinal glands had ruptured into the vena jugularis and subclavian vein and the lumens of both veins were thrombosed. Similarly, in Lücke's [20] case a lymphosarcoma of the axillary glands ruptured through the wall of the left subclavian muscles and masses of cells were partly adherent to the wall of the vessel.

Perl [21] reported a case of primary sarcoma of the wall of the inferior vena cava, and Marrassini [22] one of a primary sarcoma of the deep jugular vein.

Razzaboni [23] more recently described a case in a man of 62. The condition apparently began in the lower limb without appreciable cause and was first considered phlebitis. The rapidly increasing tumor was preoperatively diagnosed as a sarcomatous tumor of the saphenous vein. There was recurrence within about a year after operation, followed by death. Histologic examination of the tumor revealed the absence of true elastic fibers and only some very fine fibrils. It was a connective tissue tumor of the sarcomatous type probably originating in the saphenous vein and arising from an old obliterating phlebitis of the saphenous vein of the thigh but without demonstrable metastases in the lymph

17. Auffermann: Primäre Aortengeschwülste mit eigentümlichen Riesenzellen, Ztschr. f. Krebsforsch. **11**:294, 1912.

18. Miura: Riesenzell Sarcoma der Aorta, Festschr. f. R. Virchow, Berlin, G. Reimer, 1891, p. 11.

19. Schrotter: Erkrankungen der Gefässe, in Nothnagel.[6]

20. Lücke, A.: Lymphosarcoma der Achseldrüsen, Virchows Arch. f. path. Anat. **35**:524, 1866.

21. Perl: Ein Fall von Sarcoma der Vena cava inferiore, Virchows Arch. f. path. Anat. **63**:378, 1871.

22. Marrassini, cited by Razzaboni.[23]

23. Razzaboni, G.: Sarcoma primitivo della vena safena interna, Arch. ital. di chir. **11**:483, 1920.

glands. There were a few giant cells. This, the author remarked, was not a tumor of endothelial or peritheliomal type, several of which have been described in the literature and some of which have been confused with true sarcoma. Van Ree [24] reported a somewhat similar case in a woman aged 42. There was a swelling in the medial third of the left tibia. She was operated on but died fifteen days later. At autopsy the thrombosed mass was removed from the great saphenous vein and was found to be microscopically sarcomatous. There were no metastases. This was a case of phlebosarcoma racemosum.

Ernst [25] at the autopsy of a girl 19 years old found a chondrosarcoma originating in the twelfth thoracic vertebra. The tumor had invaded the renal and suprarenal veins, the vena cava and the left ovarian vein, and there were masses of tumor tissue in the lumens of both pulmonary arteries. All these were extensions of the original tumor; there were no true metastases. Warren [26] found a mass, proved later to be a chondrosarcoma, palpable above the left sacro-iliac joint in a white man of 32 years. Autopsy revealed extensions into the common iliac, left femoral and left hypogastric veins and the inferior vena cava, and there were also metastases to the lungs. The author expressed the opinion that the tumor gained access to the venous system through the branches of the left hypogastric vein and from thence readily grew into the common iliac vein, extending from there. Here, as in my case, the intravascular masses lay for the most part free within the lumen of the vessel, being only slightly adherent. The cells were in the main well differentiated and produced a large amount of cartilaginous matrix.

Egdahl [27] in 1933 reported a case of primary intravascular tumor, probably a spindle cell sarcoma, somewhat similar to that in my case. The patient, a man, had always enjoyed good health, and there was no history of syphilis or gonorrhea. About nine years before Egdahl saw him a small nodule was noticed on the anterior surface of the right wrist near the midline which grew slowly and steadily until about two years before the time of the report it was the size of a golf ball. It grew rapidly and shot out a long tortuous branch with twigs which extended nearly to the elbow. There was no pain or inconvenience until shortly before the report was written, when the wrist began to ache and the forearm became reddish blue. The condition was judged

24. Van Ree, A.: Phlebosarcoma racemosum, Nederl. tijdschr. v. geneesk. **1**: 759, 1919.

25. Ernst, P.: Ungewöhnliche Verbreitung einer Knorpelgeschwulst in der Blutbahn, Beitr. z. path. Anat. u. z. allg. Path. **28**:255, 1900.

26. Warren, S.: Chondrosarcoma with Intravascular Growth, Am. J. Path. **7**: 161 (March) 1931.

27. Egdahl, Anfin: Report of an Intravascular Sarcoma, Tr. Chicago Path. Soc. **11**:206, 1919.

to be malignant, and the tumor was removed. It shelled out easily, being covered with a glistening capsule. On examination it was found to be composed of veins filled with a firm, solid growth, but toward the tapering joints the growths easily slipped out of the veins like a finger out of a glove. The total length of the tumor was 29.5 cm., the main original portion being 7.5 cm.; the width at the widest portion was 4.5 cm. There were three radiating branches from the main tumor. The whole tumor was of firm, elastic consistency and of grayish color where cut. Microscopically, sections taken from all parts of the tumor showed as the predominant cell a spindle-shaped cell. The nucleus of the cell was fairly large, but mitotic figures were not numerous. In various places in the older part of the tumor degeneration was evident. The capsule covering the tumor and branches was found to show the histologic characteristics of a vein. On closer examination of the older part of the growth it was found that the tumor had apparently taken its origin from the wall of a blood vessel. The author was therefore led to believe that the tumor was an endothelioma but later, having had other opinions and made further examinations, he came to the conclusion that the most probable diagnosis was spindle cell sarcoma and that the site of origin was in the wall of the vein. Cells were found that could be called endothelial cells, but when two or more tissues are present in a tumor it is necessary to decide their relative importance. In Egdahl's case the spindle cells were entirely predominant in all parts of the main tumor and its branches. Much has been written in the literature on the subject of endothelioma and sarcoma, and cases of so-called endothelial growths in the veins have several times been reported, but Egdahl expressed the opinion that in practically no case has the origin of a tumor from endothelium been proved and that the continuity of a tumor with endothelium is not proof enough that it is an endothelioma. The histologic characteristics of the tumor in Egdahl's case favor the diagnosis of spindle cell sarcoma so strongly that the only possibility of its being an endothelioma would be on the assumption that the endothelial cells assumed the shape of spindle cells and appeared as fibroblastic elements, which they may at times do. But a study of the various sections would not warrant such an assumption.

In Egdahl's case there was no evidence of any invasion of a tumor from outside the vein. The growth was entirely intravascular. In my case the tissues surrounding the tumor were strongly invaded.

I am unable to find in the literature a report of any case of fibrosarcoma of the veins. It is possible that a sarcomatous tumor of the veins, either primary or secondary, may in time degenerate and thus become a fibrosarcoma, or the invading tumor tissue may already be a fibrosarcoma. However it may be, the pathologic and histologic evidence leaves no doubt that this tumor was a fibrosarcomatous invasion filling the lumen of the veins and that it was not an endothelioma.

DISCUSSION

DR. R. W. MCNEALY, Chicago: Dr. Davis has reported a case which is both unique and interesting. The usual mode of travel of metastases of sarcoma is by way of the veins. A sarcoma may arise from the walls of a vein, but authentic, carefully studied cases of this type are pathologic curiosities. In this case presented by Dr. Davis, as well as in similar cases, it seems to me that it is very difficult to be sure that the sarcomatous cells were offsprings of the mesothelial elements of veins rather than invading descendants of contiguous mesothelial tissues.

There has always been confusion in trying to separate the active rôle from the passive rôle which blood vessels play in tumors. The walls of vessels are made up of rather complex tissue, and true tumors of blood vessels are usually organoid. This does not mean, however, that individual histologic elements may not dominate to a degree which precludes a definite statement as to the tumor's exact origin.

In the case reported the tumor not only followed the course of the superficial veins but distended them in a remarkable sausage-like manner. The desmoplastic character of the tumor probably accounts for the preservation of the continuity of the strands of the tumor. Most tumor tissue is very friable and readily breaks off as emboli when a vessel is invaded.

Ewing called attention to the fact that tumors growing within vessels are permitted more freedom and often reveal their natural tendencies even more than the original tumor. One finds frequent references to intravascular growing tumors, and the distance that these tumors may extend from their sites of origin is in some cases almost unbelievable. Kellynack, in his book "Renal Growths," reported a round cell sarcoma in a boy 1½ years of age which had its origin in the kidney; the tumor broke into the renal vein and extended along it into the inferior vena cava, and thence as a thrombosis it projected into the right auricle. Instances of the extension of a tumor of the thyroid gland along the thyroid veins, jugular veins and superior vena cava into the auricle have been reported recently. Another common origin of extending intravascular growths is from tumors of the testicle. These tumors not infrequently invade the pampiniform plexus and follow the spermatic vein to the renal vein and even farther.

The histologic growth is interesting but does not offer the field for engaging speculation that is found in trying to explain the absence of demonstrable metastases in Dr. Davis' case. One can hardly conceive of this tumor growing to the extent that it did without millions of tumor cells having been cast adrift in the circulation. The low grade differentiation of the characteristic cells of this fibrosarcoma would lead one to believe that they would be very hardy and would probably survive in any except the most unfavorable environment. Undoubtedly the large majority of these vagrant tumor cells are destroyed in transit or after lodgment.

I have always been fascinated by the ability of some metastatic cells to grow in their new environment while others universally perish. In the present state of knowledge one is unable to offer any explanation of the fact that cancer of the breast gives rise to pulmonary metastases in a high percentage of cases while hepatoma, in which the growth early extends into the vessels, gives rise to pulmonary or other metastases very rarely.

It is remarkable that the patient in Dr. Davis' case still lives, and it will be interesting to follow him for a number of years to see if there is any recurrence of the tumor.

CLINICAL AND HISTOLOGIC CHANGES PRODUCED IN CARCINOMA OF THE CERVIX BY DIFFERENT AMOUNTS OF ROENTGEN RADIATION

A COMPARISON

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If any marked advance is to be made in the use of current methods for the control of carcinoma of the cervix of the uterus, it will be necessary to deliver more adequate radiation to the parametrium. Radium applied to the cervix alone is capable of controlling disease within a distance of 3 or perhaps 4 cm. from the cervical canal in most patients without completely destroying normal tissues. This fact is illustrated by the relatively high percentage of cures among patients with early stages of cancer of the cervix. However, when the parametrium or the pelvic lymphatics are involved, some other means must be employed in an attempt to deliver a sufficient dose to these regions. Roentgen irradiation is the method most frequently used for this purpose.

The response of a malignant tumor to radiation is largely dependent on the dose delivered to the diseased area and the rate at which it is administered. A small dose delivered at high intensity over a short period of time may produce changes in a tumor that are comparable to those resulting from a larger dose delivered over a longer period of time. However, owing to the fact that tissues recuperate to a certain extent after exposure to radiation, a much greater dose can be tolerated when it is delivered by means of multiple small doses than when it is administered by single prolonged heavy exposures. Whether slowly administered radiation produces a greater effect than a rapidly delivered dose is uncertain. The factor of increased total dose must be considered when a protracted treatment with multiple small doses is employed. If the rate of recuperation of tumor tissue could be shown to be less than that of normal tissues, then there would seem to be a definite advantage in employing divided doses.

During the past few years an effort has been made at the Memorial Hospital to increase the dose delivered to the tumor-bearing regions located at a distance from the zone affected by radium applied to the

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cervix alone. This has been done by increasing the target skin distance for the roentgen treatment to raise the percentage depth dose delivered at each exposure. Furthermore, a protracted treatment with multiple small exposures has been employed to increase the total dose delivered to each area, keeping the skin reaction within the limits necessary to insure complete repair. Roentgen radiation has been delivered at various rates of administration and for different total doses.

Since 1929, radium treatment to the cervix has been preceded by a cycle of roentgen irradiation of the pelvis in all but the very early cases of cancer of the cervix. Therapy with divided doses was begun in 1933. By either means the patient can be given treatment without delay, and the application of radium at a later date can be accomplished with less trauma, and often with less technical difficulty, because of the regression in the size of the primary lesion following roentgen therapy. Moreover, bleeding and discharge from the cervix are lessened, and infection is diminished. Clinical observations and repeated biopsy on material from the cervix during the roentgen treatment afford information on the effect produced in the primary tumor by the roentgen rays, and hence it may be possible to glean some knowledge of the probable effect of similar doses on cancer of the parametrium, although one cannot assume that a tumor in a different anatomic location necessarily will be affected to a similar degree. Also, the response of a given tumor to a particular method of treatment may be observed histologically, even though the dose of roentgen rays is sublethal for most cancers of the cervix.

A total of forty-nine patients [1] have been studied by serial biopsies. All received roentgen treatment before the application of radium to the cervix. Roentgen radiation was delivered at different rates of administration, over various periods of time, for different total doses. In general, this group of patients was a fairly representative cross-section of all the patients with epidermoid cancer of the cervix seen in the gynecological clinic. All histologic grades were represented, although grades 1 and 3 formed an extremely small minority. In only two of the patients was there clinical evidence that the disease was still confined to the cervix. All of the others had parametrial involvement, and six patients had very advanced cases of the disease; thus they constituted a relatively hopeless group.

In order to compare the different degrees of regression noted in the various patients after roentgen treatment alone, it is necessary to consider the dose delivered to the cervix and the time required for the administration of this amount of radiation. The dose obtained in the cervix has been determined from data presented by Arneson and

1. These patients were treated in the clinic of Dr. William Healy.

Quimby [2] and expressed in terms of threshold erythema doses. Under any circumstance the estimation of the tissue dose is only approximate. The dose delivered by roentgen irradiation was no doubt sublethal for cancer of the cervix in all but possibly one of the patients. Healy and Arneson [3] reported that the best results in the primary lesion were obtained when a minimum dose of 6 to 8 threshold erythema doses was distributed throughout its volume.

The roentgen treatment of a few patients consisted in delivering 700 roentgens in single exposures to each of four pelvic fields (two on the anterior surface and two on the posterior surface), each cutaneous field measuring about 15 cm. longitudinally and 10 cm. transversely. One treatment was given daily with an x-ray machine of 200 kilovolts at a target skin distance of 50 cm., with a filter of 0.5 mm. of copper and 2.5 mm. of aluminum. This method delivered about 0.85 threshold erythema dose to the cervix and adjacent parametrium over a period of four days. The cycle was repeated about six weeks after the radium treatment.

In 1933, a different method was adopted, in which the target skin distance was changed to 70 cm. Some of the patients included in the present series have been reported on in the previous description of this method.[4] Daily treatments of 200 roentgens were given to each of two pelvic fields. That is, the anterior and the posterior field on the left side would be treated on one day and the anterior and posterior field on the right side on the following day. This was continued until a total dose of 2,000 or 2,400 roentgens had been delivered to each area. The time of treatment required for the two total doses was three weeks and four weeks, respectively. The lesser amount of irradiation delivered about 2.5 threshold erythema doses to the cervix, and the greater amount delivered about 3.0 threshold erythema doses. The parametrium received somewhat less than the cervix.

In order to increase the rate of administration toward the end of the treatment, some patients were treated with five exposures of 200 roentgens followed by five exposures of 300 roentgens, making a total dose of 2,500 roentgens to each area. By this means about 3.1 threshold erythema doses were delivered to the primary lesion in a period of three weeks. Another group of patients were treated through six fields instead of four (two anterior, two posterior and one on each lateral surface) with daily exposures of 300 roentgens for a total dose

2. Arneson, A. N., and Quimby, E. H.: The Distribution of Roentgen Radiation Within the Average Female Pelvis for Different Physical Factors of Irradiation, Am. J. Roentgenol, to be published.

3. Healy, William P., and Arneson, A. N.: A Study of Carcinoma of the Cervical Stump, Am. J. Obst. & Gynec. **29**:370, 1935.

4. Healy, William P., and Arneson, A. N.: Radiation Treatment of Carcinoma of the Uterine Cervix, Am. J. Roentgenol. **32**:646, 1935.

of 2,100 roentgens to each area. In this method two opposite fields were irradiated each day, and the total time required for roentgen treatment was three weeks. About 3.2 threshold erythema doses were delivered to the cervix. The technic of using six fields has the advantage of delivering an even greater dose to the parametrium than to the cervix.

The radium treatment was the same for all of the patients. After the completion of the roentgen treatment an intravaginal applicator containing radon was placed against the cervix for a dose of 1,500 millicurie hours. On the following day a tandem consisting of two capsules (the lower one twice as strong as the upper one) was placed in the cervical and uterine canal for a dose of 3,000 millicurie hours. The filter in each instance was the equivalent of 2 mm. of brass. If a protracted treatment with multiple small exposures of roentgen rays was used, the patient was considered to have received complete irradiation after radium had been applied to the cervix, and no additional roentgen rays were administered. Further treatment was given only when the disease failed to disappear from the cervix or reappeared after a primary cure had been obtained. With a few patients it was necessary to apply radium to the cervix during the protracted roentgen treatment because the continued regression of the lesion and the contraction of the cervix threatened to increase markedly the technical difficulty of subsequent applications of radium. No detailed study has been made by biopsies after the treatment with radium, because complete destruction of the disease usually followed.

CLINICAL TYPE AND RESPONSE TO IRRADIATION

The patients presented a variety of different types of cervical lesions. Some were of an everting type of growth, cauliflower-like, usually soft, bulky, friable, vascular and sometimes ulcerated. Others were of an infiltrative type, usually hard, moderately bulky, sometimes nodular, frequently ulcerated and often infected. A few patients presented lesions which had completely destroyed the cervix, the latter having sloughed away, leaving an excavated, ulcerated, badly infected crater. The cauliflower-like and the infiltrative lesions seem to be distinct types. The cratered lesions, on the other hand, may have begun as either of the two varieties. As the disease progressed and the infection increased, the cervix sloughed away, leaving a crater. This explanation is substantiated by the fact that several of the patients gave a history of sudden hemorrhages, which may have marked the instant at which a large portion of the cervix was thrown off. One would therefore expect the cratered lesions to be more advanced than the other types. In general this was found to be true.

It is difficult to determine clinical criteria indicative of the response which a tumor may be expected to show under irradiation. The final

result after treatment is, of course, largely dependent on the stage of involvement to which the disease has progressed. However, there was a sufficiently marked difference in the response to treatment shown by the various types to warrant a discussion of these facts, despite the small number of patients in the series.

As was stated before, all of the patients received roentgen treatment before the application of radium to the cervix. They were observed carefully during the time that external irradiation was being given, and each patient has been examined at intervals ever since. The estimation of the degree of regression by clinical examination rests on individual interpretation, and results are consequently subject to error. Not only must the original condition of the diseased area be considered but the amount of radiation delivered to the tumor and the rate at which it was administered, when one attempts clinically to evaluate the response.

TABLE 1.—*Degree of Regression Noted in Primary Lesion After Roentgen Treatment Only and Present Condition of Patients After Complete Treatment According to Type of Lesion*

Type of Lesion	Number of Patients	Regression in Cervix from Roentgen Treatment Only			Present Condition after Roentgen and Radium Treatment		
		Good	Fair	Poor	Good	Fair	Poor
Cauliflower-like	23	19	4	0	17	4	2
Infiltrative	18	6	10	2	11	4	3
Cratered	8	1	3	4	2	1	5

Moreover, the patients have been treated too recently to make any definite statement as to the final result after treatment with radium. This is not important in the present study, since we are interested only in primary responses. However, it can be demonstrated that a greater percentage of the cauliflower-like lesions showed a good response to external irradiation and have remained in good condition up to the present time than of either the infiltrative or cratered types.

There were twenty-three patients (47 per cent of the group) who had cauliflower-like lesions. In nineteen of these patients the tumor showed good regression from roentgen treatment only, as manifested by shrinkage and contraction of the lesion. At the present time seventeen of these patients are in good condition following the completion of their treatment by the application of radium to the cervix. There were eighteen patients with infiltrative lesions, and in six the tumor showed good regression from roentgen rays. Eleven are now in good condition. Among the eight patients with cratered lesions, only one showed a good response to external irradiation, and only two are in good condition at the present time. These results are shown in table 1.

The poor results obtained in the group of patients with cratered lesions may be explained partially by the fact that these lesions usually

were more advanced than the other types. Infection and ulceration were also more marked in this group, and these factors sometimes complicated the course of the disease during treatment. The cauliflower-like lesions, on the other hand, presented a different situation. These lesions, more polypoid in form, did not infiltrate the fibrous stroma. They were more papillary in structure, and evidently they were nourished by a less stable blood supply. There were less infection and ulceration than in the other types. These factors probably contributed to the good response which most of these patients showed to treatment. However, this may not necessarily imply that a cauliflower-like lesion has a better eventual prognosis than other types.

Aside from the clinical evidence of regression, the changes produced in the different lesions can be studied also from repeated biopsies. Thirteen of the twenty-three cauliflower-like lesions showed marked changes, while nine of the infiltrative and three of the cratered types revealed a comparable alteration from roentgen irradiation. When expressed in percentages, the difference in the response to treatment, as shown by histologic study in the three types, was not as great as that observed clinically. This indicates that the clinical character of the lesion is more important in estimating the radiosensitivity of the local disease than are serial biopsies.

The total dose and the rate of administration of radiation also influence the degree and rapidity with which the tumor regresses. The patients have been grouped according to the method used for delivering roentgen rays, irrespective of the appearance of the primary lesion. There were nine patients who received 0.8 threshold erythema dose in the cervix over a period of four days, seven who received 2.5 threshold erythema doses in three weeks, thirteen who received 3 threshold erythema doses in four weeks, ten who received 3.1 threshold erythema doses in three weeks and ten who received 3.2 threshold erythema doses in three weeks.

Of the nine patients who received the smallest amount of roentgen radiation, in only one did the tumor show evidence of good histologic regression. Among the seven patients who received 2.5 threshold erythema doses in the cervix over a period of three weeks, in three the tumor showed good regression and of the thirteen who received 3 threshold erythema doses over a period of four weeks, in five the tumor showed good regression. In both of these last two groups about 40 per cent of the patients showed evidence of marked histologic changes from external irradiation. However, the patients who received a greater amount of radiation, that is, 3.1 and 3.2 threshold erythema doses, evidenced a greater percentage of marked changes in a shorter period of time (three weeks). These results are shown in table 2. Of the ten patients who received 3.1 threshold erythema doses in six (60

per cent) the tumor showed good histologic regression. In eight of the ten who received 3.2 threshold erythema doses (80 per cent), the tumor showed good histologic regression.

The patients in the group receiving 3.1 and 3.2 threshold erythema doses at the depth of the cervix within a period of three weeks developed the most marked cutaneous reactions. However, the damage to the skin remained within the limits of tolerance, and there was complete repair shortly after the treatment was finished. It is impossible to determine an optimum dose and rate of administration from the present knowledge of the recuperation of normal tissues and of tumor tissues. In the absence of such information and from the data obtained here on the regression of the primary lesion resulting from different methods of external irradiation, it would seem advisable to employ some form of protracted treatment delivering a large total dose at a fairly rapid rate of administration over a moderately short period of time.

TABLE 2.—*Histologic Changes Noted in Primary Lesion According to the Amount of Radiation Delivered to the Cervix by External Irradiation*

Dose Delivered to Cervix by Roentgen Irradiation Only	Number of Patients	Histologic Evidence of Regression		
		Good	Fair	Poor
0.8 threshold erythema doses in 4 days.....	9	1	2	6
2.5 threshold erythema doses in 3 weeks.....	7	3	1	3
3.0 threshold erythema doses in 4 weeks.....	13	5	6	2
3.1 threshold erythema doses in 3 weeks.....	10	6	3	1
3.2 threshold erythema doses in 3 weeks.....	10	8	1	1

CORRELATION OF THE DEGREE OF HISTOLOGIC CHANGES WITH THE CLINICAL REGRESSION NOTED IN THE CERVIX AND THE PRESENT CONDITION OF THE PATIENTS

As was stated previously, in each instance the primary lesion received a sublethal dose from external irradiation, with the possible exception of one. Moreover, the cervix was not destroyed in any patient by roentgen treatment. Because of the incomplete destruction of the cervix it is possible to correlate the histologic and clinical changes resulting from the roentgen rays. It has already been shown that varying percentages of marked histologic changes were obtained from different amounts of external irradiation. However, it is more difficult to correlate the histologic changes produced by the roentgen rays with the condition of the patients after the application of radium, because destruction of the cervix usually resulted thereafter, and the immediate results were more or less uniform. That is, the present condition of the patients who received 0.8 threshold erythema dose in the primary lesion from roentgen treatment is not markedly different from that of those who received 3.2 threshold erythema doses. The changes in the cervix were minimal in the group that received the smallest amount of

external irradiation, until after radium was applied. Because of the fact that most of the treatment delivered to the primary lesion in this group was with radium and because of the relative uniformity of the early results after the application of radium, these patients have been excluded from the comparison of the histologic changes with the clinical evidence of regression of the tumor from external irradiation and the present condition of the same patients. It may be expected, however, that a greater effect was produced in the parametrium beyond the radius of the action of radium applied to the cervix in the patients who received the greater amount of roentgen treatment.

Forty patients were treated with multiple exposures of roentgen radiation. In twenty-two of this number, the tumor showed evidence

TABLE 3.—*Degree of Regression Noted Clinically in the Cervix for the Patients with Tumors Showing Good, Fair and Poor Histologic Regression and the Present Condition of the Patients*

Histologic Regression in Patients Treated by Divided Doses of Roentgen Rays	Number of Patients	Regression in Cervix from Roentgen Treatment Only	Present Condition after Roentgen and Radium Treatment		
			Good	Fair	Poor
Good	22	Good (19 patients)	15	1	3
		Fair (3 patients)	3	0	0
Fair	11	Good (8 patients)	7	1	0
		Fair (3 patients)	2	0	1
Poor	7	Good (2 patients)	0	1	1
		Fair (2 patients)	0	0	2
		Poor (3 patients)	0	1	2

of good histologic regression. In eleven there were fairly good changes, and in seven the effect was poor. Among those who showed good changes, nineteen had good clinical regression of the tumor, and fifteen are now in good condition. Three showed only fair clinical changes but are now in good condition. Of the eleven who had fair histologic changes, eight showed a marked clinical response, of whom seven are now in good condition, and three showed a fair clinical change, of whom two are now in good condition. If the histologic change was poor (seven patients) a less marked change was noted clinically and the present condition is less satisfactory. These results are shown in table 3.

Since the correlation between clinical and histologic regression is imperfect, there must be some factors not ascertainable from biopsy which determine the degree of change from irradiation. If the treatment is adequate and the lesion is of the cauliflower-like type, the histologic changes are apt to be marked. If the histologic changes are marked, the clinical evidence of regression is usually good as well as the immediate results after complete treatment. Infection may play a part

in the response of the tumor, but the extent to which the disease has advanced is by far the most important factor.

PATHOLOGIC OBSERVATIONS

In a previous paper,[5] attention was called to the fact that little could be ascertained concerning the radiosensitivity of cervical carcinoma under methods of treatment then in vogue. It was believed that no significant quantitative data could be obtained concerning the radiosensitivity of the tumors when the therapeutic procedures employed involved the local application of quantities of radium directly to the lesion in doses which were certainly far beyond the lethal amount of radiation for a tumor near the applicator and far below that amount for a tumor situated at a few centimeters distant. Likewise it was considered probable that such data could be obtained, provided the tumors were treated with more uniform external irradiation of a type which would deliver more evenly distributed radiation throughout the tumor. Hence when the present clinical investigation was undertaken it was accompanied by the effort to determine, if possible, the differences in the response of histologically different epidermoid carcinomas.

Unfortunately, however, the patients available for this kind of treatment presented tumors very similar in histologic type. Practically all were rather typical plexiform epidermoid carcinomas (grade 2). Hence the group was unsuitable for determining differences, provided they exist, in the responses of different types. However, such decided differences appear to exist in the behavior toward radiation of comparable histologic types in different persons that we are forced to conclude that in a case of plexiform epidermoid carcinoma of the cervix a single biopsy is essentially useless for the estimation of the probable local clinical response to radiation. By local clinical response we mean that response to external irradiation alone given by the methods and in the doses described prior to the application of radium.

Apparently, as judged by our results, the response most to be desired from roentgen treatment with divided doses consists in what we prefer to call a progressive squamous degeneration. This term we employ to designate a series of changes characterized by swelling of the tumor cells, ballooning degeneration or pyknotic fragmentation of nuclei, a progressively increasing cytoplasmic opacity and acidophilia, a tendency to cornification, necrosis, leukocytic infiltration and slough, often followed by a foreign body giant cell reaction to necrotic squamous pearls and occasionally by calcification. The process seems to begin in a punctate fashion in single cells or in groups of two or three cells and rapidly spreads to involve the entire thickness of the individual

5. Stewart, Fred W.: Radiosensitivity of Tumors, Arch. Surg. **27**:979 (Dec.) 1933.

sheets comprising the cancerous epithelium. In the relatively undifferentiated plexiform tumors, there is little evidence for believing that the process is a progressive degenerative differentiation from a basal layer of mother cells; the entire thickness of the carcinomatous epithelium seems equally involved. Figures 1 to 4 illustrate the process as observed in a single case by successive biopsies. It seems to us unnecessary to give once more the histologic description of this process. It is well known,

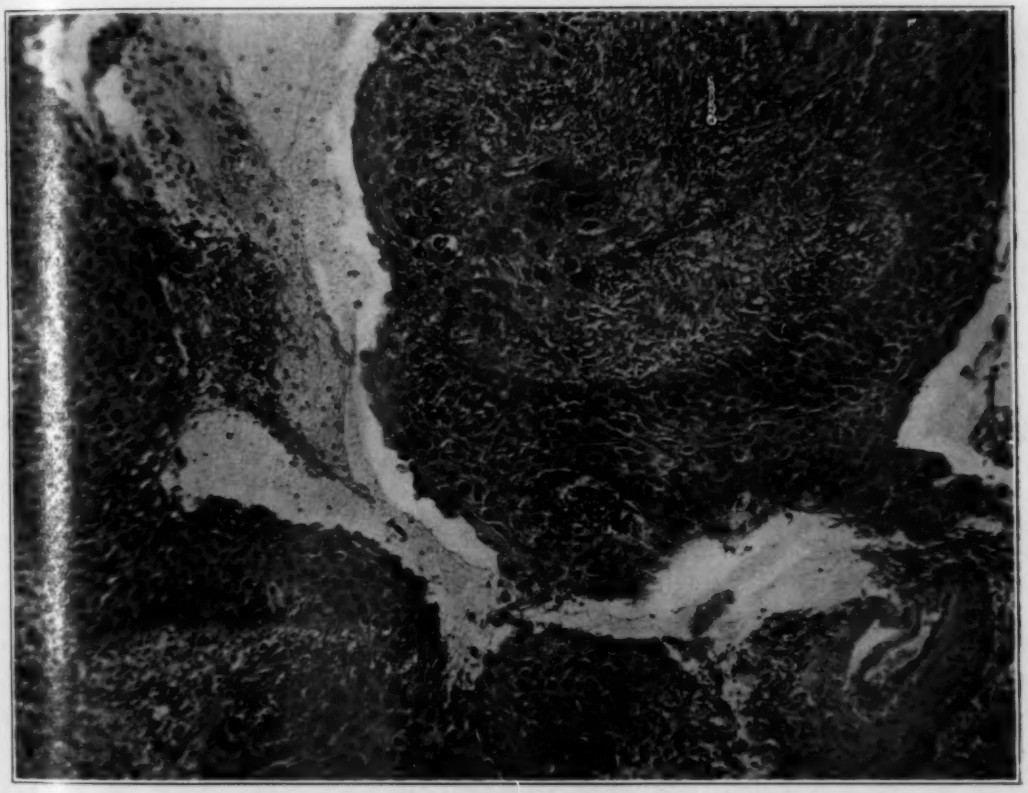

Fig. 1.—Plexiform epidermoid carcinoma of the cervix, grade 2.

particularly from the papers of Dustin [6] and the more recent work of Frola.[7] In rare cases in the present series this progressive squamous

6. Dustin, A. P.: Contribution à l'étude radiobiologique des épithéliomas du col utérin traités par la télécuriethérapie. Les courbes de pycnoses, de mitoses normales et de mitoses atypiques, Bull. Acad. roy. de méd. de Belgique **7**:237 (March 26) 1927. Dustin, A. P.: Nouvelle contribution à l'étude radiologique des épithéliomas du col utérin soumis à la télécuriethérapie, Arch. internat. de méd. expér. **3**:383, 1927.

7. Frola, Goffredo: Etude histologique et radiobiologique des tumeurs du col utérin traitées par la radiumthérapie, Arch. internat. de méd. expér. **8**:289, 1933.

degeneration has proceeded to a point at which repeated biopsies showed no tumor and at which there was good reason to believe that a local cure had been obtained, although subsequent radium treatment was not omitted for this reason.

Unfortunately, however, the results of even serial biopsies are uncertain evidence of wholly favorable response on the part of the tumor. It is not infrequent after a series of biopsies in which the

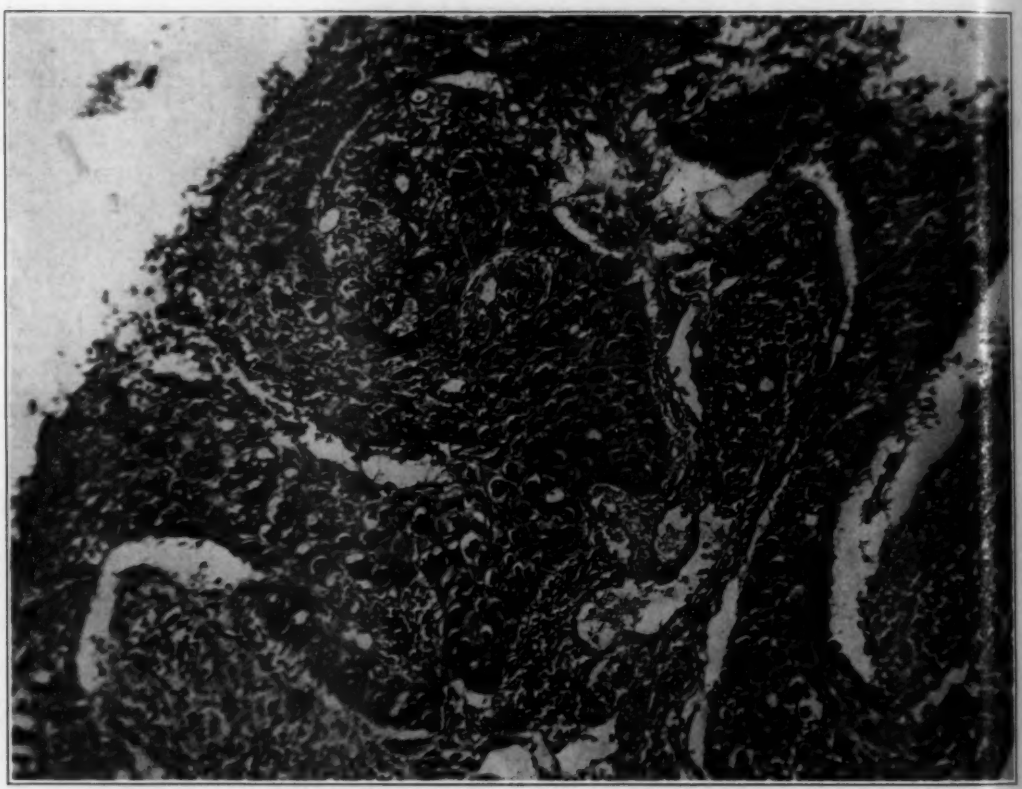

Fig. 2.—The tumor shown in figure 1 after application of about 0.5 threshold erythema dose by external irradiation.

earlier specimens, obtained from shortly after the time the treatment began until doses of from 1 to 1.5 threshold erythema doses had been administered, showed a very favorable progress toward squamous degeneration, that the regressive phenomena cease and further biopsies show little or no alteration in the tumor. One is tempted to assume that observations of this sort must be considered evidence of radio-immunization of the tumor. In fact, on this basis a small series of patients was treated by progressively increasing doses in the belief that

an increase in the daily dose might overcome this radio-immunization and produce an orderly sequence of degenerative changes in the tumor which might not have occurred under constant daily doses. The patients who have been treated in this fashion are too few to permit any conclusion. We feel that it is desirable to treat a representative series of patients with cancer of the cervix in this fashion, but at the same time we must question the evidence on which the advisability of such methods of therapy has been suggested.

Material for biopsy is obtained from surfaces only of cervical carcinomas. Often the surfaces are ulcerated and infected. Spontaneous degeneration is common. It appears that radiation delivered to areas where there is a marked tendency to spontaneous degeneration and slough will often produce changes which will lead to an exaggerated notion of the effect in progress in less unstable portions of the tumor. It may well be that the appearances first interpreted by us as evidence of progressive radio-immunization are merely due to a chance selection of the specimen for biopsy; i. e., the material for the earlier biopsies was taken from superficial areas tending to spontaneous degeneration, and that for the later ones, showing little or no change, from deeper well nourished areas, as the tumor regressed and infection diminished.

This alternate explanation formulated, instead of one radio-immunization one finds support in two phenomena frequently observed in the course of serial biopsies. The first is the distribution of the effect of radiation in the tumors. Even in biopsies of small sections which rarely have a diameter exceeding 2 to 4 mm., it is readily observed that the changes due to the radiation may be very irregularly distributed. They may range from almost no alteration to nearly complete squamous degeneration. Such variations may be apparent within the range of a few microns. We have sought the explanation for these differences within narrow ranges in the irregular effects on the capillaries or in the irregularity of capillary distribution, but we have found no evidence for the direct support of this interpretation. When a tendency toward adult squamous differentiation exists in small foci of an otherwise relatively undifferentiated tumor, the maturation under radiation is most marked in those areas, and this may explain the focal character of the changes. This interpretation is quite consistent with observations on the effectiveness of roentgen therapy with divided doses on relatively differentiated, spontaneously maturing squamous carcinoma, repeatedly emphasized by the Paris school of radiologists. Hence it is probable that the condition is not radio-immunization in the sense that certain alterations take place to a given degree beyond which further radiation in similar doses fails to increase the degeneration, but that the areas which remain essentially unaltered by treatment represent portions of the tumor which with the doses employed for some reason escaped any

alteration. That such areas are not immune to larger doses appears from the fact that in most instances residua of the tumor after roentgen treatment responded in a normal fashion to radium.

Furthermore, we have observed repeatedly that even though serial biopsies show progressive degeneration of the tumor, nevertheless, if a delay of one to six weeks occurs between the date of the termination of roentgen treatment and the insertion of radium, a biopsy usually shows fully active carcinoma which in most instances cannot be distinguished

Fig. 3.—The tumor shown in figure 1 after application of a little less than 3.0 threshold erythema doses.

from the initial tumor. Since it is highly improbable that recurrences take place from portions of the tumor which have shown any decided advance in the direction of squamous degeneration, we are forced to conclude that parts of the primary lesion regularly escape degeneration with doses which are lethal or nearly lethal for other portions. Thus we have no justification for believing that the condition is radio-immunization or that the disease, influenced by constant daily doses up to a certain state of degeneration, would be influenced more markedly

by a process of pyramiding the daily dose, although we feel the desirability for more extensive experimentation with such methods.

Frola offered an interesting interpretation of these recurrences during the course of apparently satisfactory regression of a tumor due to irradiation. However, it is one which we cannot accept. Frola gave particular attention to the irradiated cervical mucous glands. He called attention to the bizarre appearances of these glands when areas or plaques of metaplastic epidermoid cells interrupt the columnar cell

Fig. 4.—The tumor shown in figure 1 after application of 3.2 threshold erythema doses. The lesion has disappeared except for a few degenerated squamous cells along the mid-border on the left.

layer. Apparently Frola is of the opinion that irradiation produces these metaplasias and that they may go on to the production of cancer. Hence he would see in the recurrences after irradiation a neogenesis of tumor at the expense of cervical mucous glands rendered metaplastic by the irradiation. He stated:

Tous ces phénomènes . . . s'observent vers la fin du traitement curiethérapique, après que plusieurs biopsies nous ont montré la disparition ou la nécrose avancée de la tumeur initiale. Les phénomènes si intéressants que nous avons pu

démontrer ne s'arrêtent pas ici. On peut parfois constater aux dépens des cellules mucipares métaplasiées ou des cellules normales des glandes elles-mêmes, des phénomènes qui dépassent la simple métaplasie pour arriver à la véritable cancérisation. On assiste alors à la formation d'un véritable épithélioma spinocellulaire d'aspect morphologiquement semblable à celui de la néoplasie préexistante.

(All these phenomena are observed toward the end of the radium therapy, after many biopsies have shown us disappearance or advanced necrosis of the original tumor. The interesting phenomena which we have been able to show do not end here. One sometimes sees, at the expense of the metaplastic mucous cells or of the normal cells of the glands themselves, phenomena which go beyond simple metaplasia and into true cancer. One witnesses then the formation of a true spindle cell epithelioma with a morphologic picture like that of the preexistent neoplasm.)

We believe that the evidence from our own seriès does not support Frola's contention but that certain of the phenomena observed may be the result of degeneration of areas of metaplasia caused by roentgen radiation, that others represent degenerative phenomena in persistent cancer lining the ducts of cervical mucous glands, and that there is no evidence for the assumption of neogenesis of tumor from such areas provided one uses the term to imply the formation of a new cancer under the influence of irradiation. Admitting the truth of Frola's statement that many cancers are the result of irradiation, it scarcely can be said that the factor of time which operates in the irradiation of cervical cancer is in any way comparable to those operative in the genesis of roentgen ray carcinoma. The majority of the histologic appearances observed by Frola represent undestroyed foci of cancer lining cervical glands. When the degenerative change is marked, there is no evidence that such foci regenerate active cancer. The regeneration proceeds from foci damaged to a much less degree, although there necessarily must be a point at which the balance between destruction of and capacity to regenerate local tumor is very delicate. The most interesting phenomenon in reference to the cervical glands is their ability to persist unaltered in the face of irradiation sufficient to destroy completely some carcinomas of the cervix. When recurrences of the carcinoma take place, their histologic picture usually entirely duplicates that of the original tumor. This would scarcely be so regularly the case if one were dealing with some such mechanism as Frola suggests. In our opinion they so closely resemble the original tumor merely because the original tumor was never destroyed, despite the evidence to the contrary from the normal results of one or more biopsies (figs. 5 to 7).

The initial biopsy, as we have previously intimated, offers no features which enable us to predict that under external irradiation the tumor will undergo an orderly progressive degeneration; nor does it, as a rule, offer an explanation for the failure for such evolution. However, serial biopsies occasionally show a series of events in the evolution of the

tissue under treatment which, even though they themselves lack explanation, may account for the failure of the tumor to show further satisfactory regression.

In a sense, these phenomena might well be considered a type of radio-immunization with alteration in structure toward histologic varieties usually considered as being more radioresistant tumors. The following case may be used as an example of this sort of change in structure.

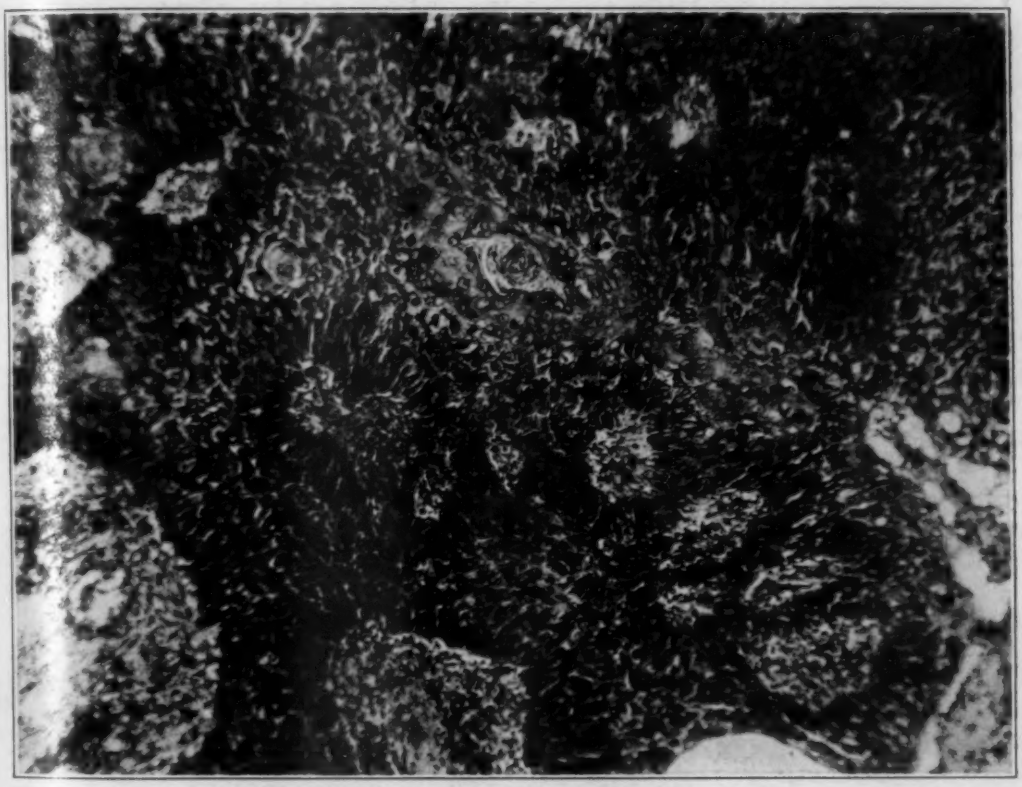

Fig. 5.—Plexiform epidermoid carcinoma, grade 2.

CASE 1.—M. B. presented a primary tumor, an advanced cauliflower-like lesion, 5 cm. in diameter, filling the vaginal vault and ulcerated. Histologic examination showed a diffuse anaplastic, small cell plexiform epidermoid carcinoma of grade 3. There was only a trace of spindle cell structure. The tumor was infected, and the interstices between the tumor cells were filled with polymorphonuclear leukocytes (fig. 8).

A biopsy made after 1 threshold erythema dose of roentgen rays had been applied showed the cells slightly larger, the cytoplasm pinkish and more opaque and plasma cells appearing in the exudate. After 2 threshold erythema doses, there was fairly marked squamous degeneration. The cells were large and loose and

appeared not unlike decidua. An increased tendency toward spindle cell change was noted, and atypical tumor giant cells appeared. After the application of 2.5 threshold erythema doses, the cytoplasmic opacity had increased still further, and the spindle cell structure was very decided (fig. 9). A biopsy after 3 threshold erythema doses had been given showed a less marked stage of alteration; a second examination showed slough only, but a third showed the tumor to be made up of atypical polyhedral spindle and squamous cells lying in the midst of thick hyaline tissue (fig. 10), probably a product of the degenerating tumor. A biopsy of a section secured two weeks later showed, in addition to this spindle cell structure,

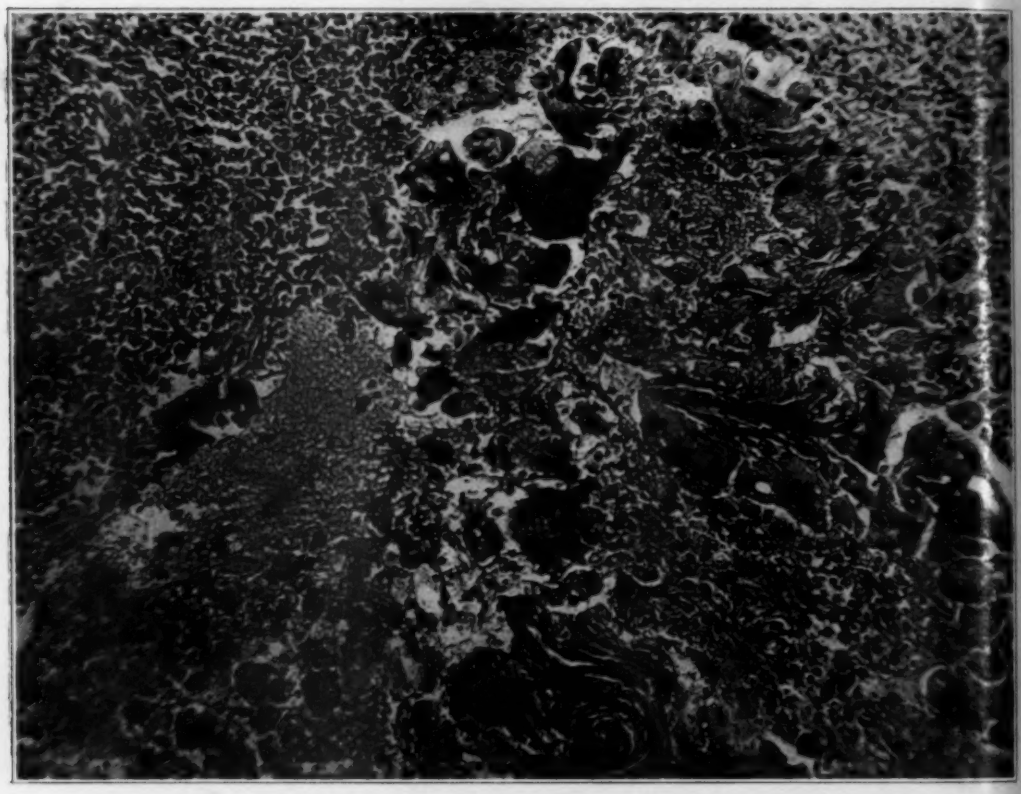

Fig. 6.—The tumor shown in figure 5 after application of about 3 threshold erythema doses. The biopsy shows only masses of degenerated sloughing squamous cells.

a small area of fully active cancer and a focus resembling low grade adult squamous carcinoma (fig. 11). Furthermore, even after application of radium for a dose estimated at about 10 threshold erythema doses additional to the site from which the biopsy specimen was taken, disease persisted in the cervix, finally resembling in structure the original tumor.

In two other cases successive biopsies showed areas of tumor, in one instance resembling adult squamous carcinoma and in the other scarcely more than adult papilloma. It is open to question whether in

these three cases we observed regressive changes in what were originally homogeneous anaplastic or plexiform carcinomas leading to the development of adult forms or whether we were dealing with mixtures of types from the beginning. On the one hand, pathologists who are familiar with the changes produced by irradiation in tumors are well acquainted with the phenomenon of physiologic maturation as part of regression due to irradiation. On the other hand, it is quite possible

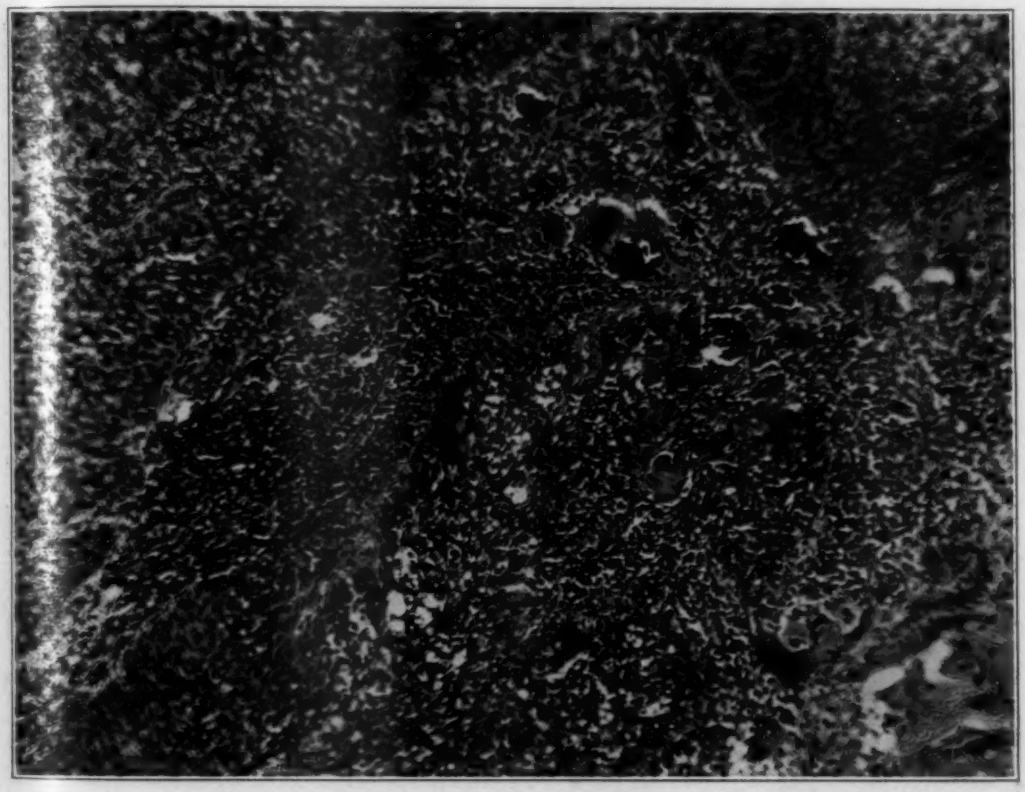

Fig. 7.—The tumor shown in figure 5 four weeks after application of 3 threshold erythema doses. Residual degenerated calcified squamous cells are surrounded by fully viable tumor, not distinguishable from the original tumor.

that the structure of the original lesion was complex. From the study of the biopsies we are inclined to interpret the spindle cell metaplasia with hyaline degeneration as the result of irradiation, and we are inclined to doubt the development of fully adult forms of the carcinoma following irradiation, although it may be that in areas where the tendency to form adult cells was marked in the original tumor there was an accentuation of the process under irradiation. That irradiation may produce a peculiar spindle cell metaplasia accompanied with very

marked radioresistance almost amounting to an absolute insusceptibility to radium has been known in the case of certain carcinomas developing on the basis of chronic roentgen ray dermatitis. In cervical cancers in which these phenomena were encountered, the appearances were only temporary. Hence it is unlikely that the failure to respond to treatment was more than temporarily influenced by the alteration in structure, since successive biopsies showed a return to the original structure.

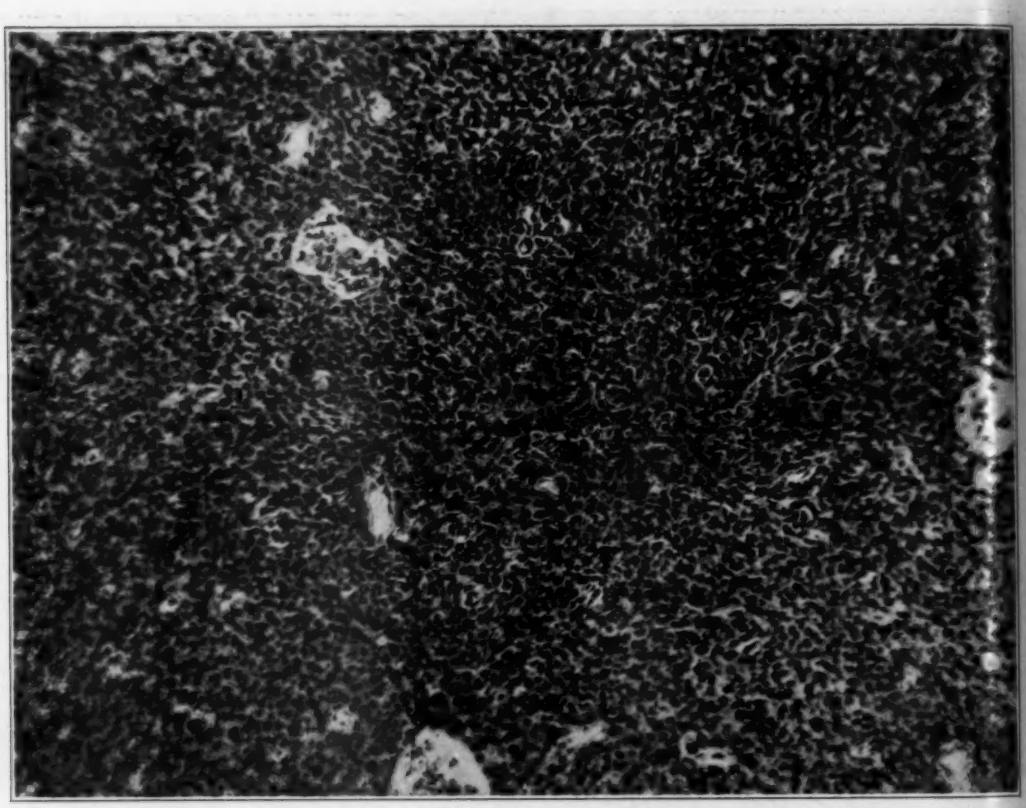

Fig. 8.—Anaplastic diffuse epidermoid carcinoma, grade 3.

Material is insufficient to determine whether any particular type of cervical carcinoma tends to undergo spindle cell metaplasia under irradiation. As a rule, we perform only a single biopsy prior to treatment. That is insufficient to give any idea of what structural varieties may be present in different areas of the tumor. The possibility suggested itself to us that spindle cell metaplasia might be expected to occur in cases in which in the original tumor there was a tendency to perilobular keratinization, as in tumors of the type described by Regaud and

Gricouroff [8] as *épithélioma épidermoïde à kératinisation périlobulaire* or as *épithélioma pavimenteux stratifié, à évolution épidermoïde, à transformation cornée péricordonale.* This would be in line with Krompecher's [9] description of spindle cell carcinomas originating in an elongation of the basal cell. We have been unable to support this thesis. It does appear to be a fact that spindle cell metaplasia is most often associated with the fungating cauliflower-like type of tumor.

Fig. 9.—The tumor shown in figure 8 after application of about 2 threshold erythema doses. Spindle cell metaplasia is present.

Spindle cell areas alone do not appear to be a criterion for determining increased radioresistance. We emphasized spindle cell metaplasia accompanied by a peculiar hyaline production which is probably a stage of beginning abortive fibrosis. We feel that variations in the resistance in these relatively undifferentiated types of cervical carcinoma

8. Regaud, C., and Gricouroff, G.: L'épithélioma épidermoïde du col de l'utérus à kératinisation périlobulaire, Ann. Surg. **93**:360, 1931.

9. Krompecher, E.: Der drüsenartige Oberflächenepithelialkrebs: Carcinoma epitheliale adenoides, Beitr. z. path. Anat. u. z. allg. Path. **28**:1, 1900.

for the most part must lie in features of the tumor not ascertainable from superficial biopsy. The most marked resistance noted in this series seemed to be that of a patient with a positive Wassermann reaction. This agrees with the observations on the radioresistance of lingual carcinoma associated with syphilitic glossitis. The most sensitive tumor occurred in a patient who was pregnant. Biopsy failed to show significant differences in the types of tumor in these two patients.

Fig. 10.—The tumor shown in figure 8 after about 3 threshold erythema doses. Spindle cell metaplasia, hyaline degeneration and beginning abortive fibrosis are seen.

As is readily seen from the tables, in the majority of patients treated with divided doses there was very decided regression of tumors from external irradiation alone, and there was a definite tendency in most cases for the clinical regression to parallel the histologic evidence of alteration. However, in a few cases the phenomena diverged. In such cases the clinical result appeared more impressive than the histologic result. It may be well to cite a case in point.

CASE 2.—B. C. presented an advanced, ulcerated, cauliflower-like lesion filling the vaginal vault. Histologic examination showed a typical plexiform epidermoid carcinoma. The blood supply, so far as could be ascertained from biopsy, was delicate. Lymphoid stroma was present. There was a polymorphonuclear exudate over the ulcerated surface. After 0.5 threshold erythema dose of roentgen rays the lymphoid infiltration was more marked. The cells became somewhat larger and more opaque. The mitoses averaged one per field (high power). The changes in general were slight. After 1 threshold erythema dose, slight squamous degeneration occurred. Degenerative giant cells were present. There was a slight tendency to spindle cell metaplasia and no reduction in mitoses. After 1.5 threshold erythema doses, there were decided differences in various portions of even a small section taken for biopsy. Some areas showed moderately advanced squamous degeneration. Others showed no changes from the original status. After 1.5 threshold erythema doses (second biopsy) there was little change; many plasma cells appeared and the spindle cell areas were more marked. After 2.5 threshold erythema doses there was no change. After 3 threshold erythema doses the tumor was essentially unaltered. Twelve days and seventeen days after 3 threshold erythema doses the tumor was unaltered.

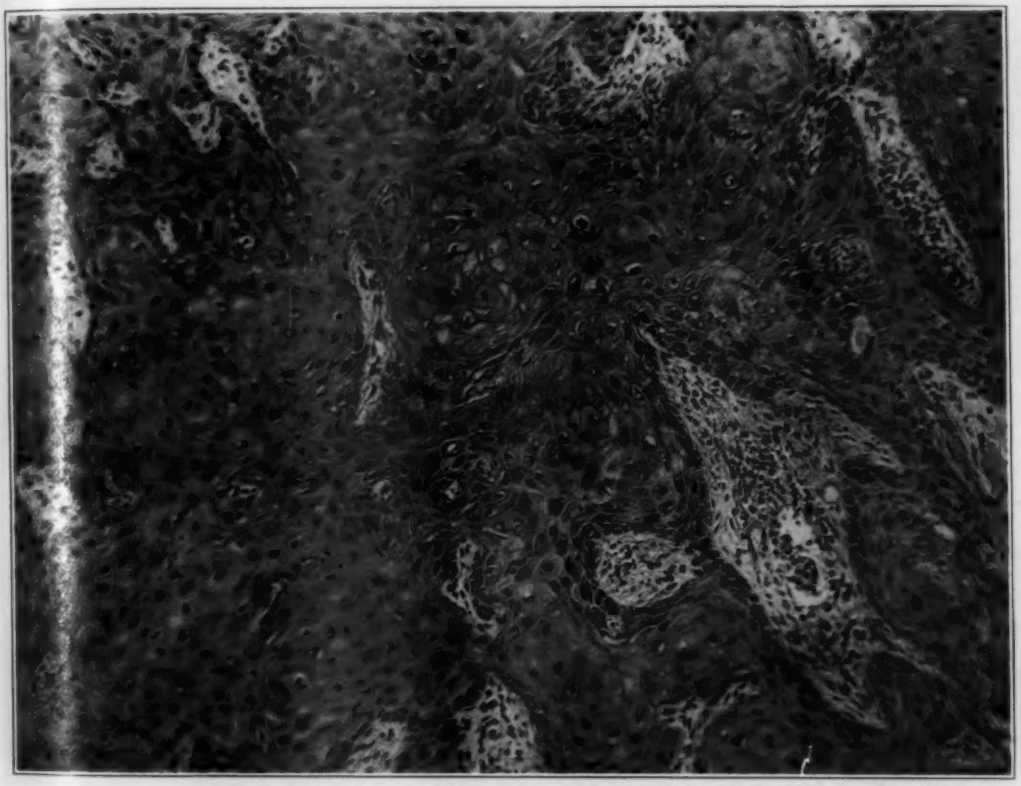

Fig. 11.—The tumor shown in figure 8 three weeks after application of about 3 threshold erythema doses. It is now an adult squamous cancer.

Despite the unsatisfactory character of the histologic change during treatment, the clinical result was described as "good regression from roentgen treatment; cervix completely healed after treatment with radium but hard and nodular." Six months after radium treatment a membrane developed over the cervix, hemorrhage occurred, and a rectovaginal fistula developed, but no evidence of disease could be found. It is difficult to understand how a tumor can regress well clinically and

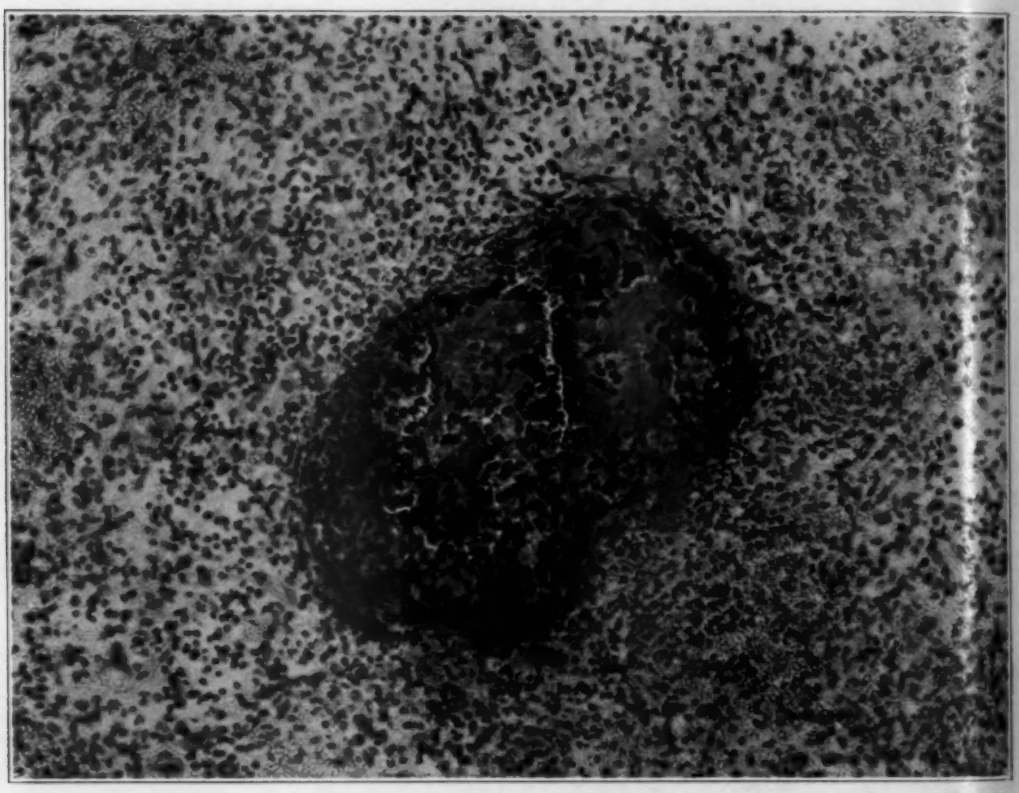

Fig. 12.—Anaplastic epidermoid carcinoma, showing degeneration in the midst of acute exudative inflammation and isolated clusters of naked hyperchromatic nuclei in the midst of degenerative hyaline tissue.

yet retain a histologic character closely resembling its original appearance. Diminution in infection is scarcely sufficient to explain the phenomenon, and we are inclined to interpret it as a result of the chance selection of the material for biopsy, or the selection of material from the most unaltered part of the lesion for section. Suffice it to say that repeated biopsies indicating no essential histologic changes in the structure of a tumor during treatment may not necessarily mean that no clinical reduction is occurring.

We have dealt up to the present time with the histologic features involved in the regression of the typical plexiform epidermoid carcinoma of the cervix (called basal cell carcinoma or transitional cell cancer in certain clinics). As we stated, during the time of the present investigation our material consisted almost entirely of such types. Hence we have little information on the processes of regression of certain very anaplastic carcinomas. The type of regression of these varieties is probably not uniform. We found one tumor radioresistant and undergoing spindle cell metaplasia with hyaline degeneration and beginning abortive fibrosis. Another, however, seemed to disappear by breaking up into small clusters of almost hyperchromatic naked nuclei in the midst of degenerative hyaline material, accompanied by an acute exudative inflammation (fig. 12). Whether or not this is a common type of change due to radiation in tumors of this variety cannot be stated without much more evidence. The material taken for biopsy included a very small number of tumors probably originating in and duplicating in an abortive fashion the ducts of cervical glands (pseudoglandular types). It was thought that these might prove more radioresistant, but this has not proved to be the case.

COMMENT

At the beginning of this paper mention was made of the necessity of increasing the dose of the roentgen rays to the parametrium if any marked improvement was to be made in the cure of cervical cancer. The clinical and pathologic changes following different amounts of external radiation delivered to the primary tumors of the cervix were studied in the hope that they might prove an index to what was going on in the parametrial extensions. Two facts seem definite. First, the quantity of external radiation introduced into the primary tumor by the methods so far employed will not cure more than a very small percentage of cervical carcinomas. Hence we are forced to the conclusion that by such methods cure of parametrial disease of established character will be equally rare. Second, it is unlikely that doses to the parametrium of the order considered in this paper will lead to any marked degree of restraint in growth in the average case, since observations on primary tumors indicate that after nonlethal doses of roentgen rays recurrence of the tumor in its original histologic form is rapid.

On the other hand, there is both histologic and clinical evidence of very marked regression of these primary lesions, and the necessary conclusion must be that different parts of the primary lesion undergo regression under different quantities of radiation even though the fundamental histologic structure is relatively similar throughout. There is a very decided difference in the order of the dose which will produce marked regression clinically and that which will produce complete histo-

logic sterilization. Since histologic observations indicate that differences in the extent of destruction of the tumor may exist even in very small areas it may be possible that in the exceptional instances of early stages of parametrial cancer, the recent unestablished nodular embolus, a dose of the order possible by the present method of external irradiation with divided doses will result in a cure, but such a favorable series of circumstances would be a rarity. Cure of an established parametrial extension of the average cervical cancer cannot be anticipated with external irradiation in the amount heretofore given. It may possibly cure exceptional, highly sensitive tumors.

The question arises whether under such circumstances it is worth while to pursue a protracted course of external irradiation. We are of the opinion that it is, not because it will result in a decided increase in the curability of the average cervical cancer but because it may be a factor of decisive importance in an occasional case. There is a large gap between the 3.2 threshold erythema doses delivered by the present method and the 6 to 8 threshold erythema doses which we found most effective in radium treatment of the average primary cervical cancer. It is very possible to close this gap partially if one is willing to accept a greater degree of initial cutaneous reaction and rectal and vesical irritation as the dose delivered by external irradiation is increased. Although this may be unwarranted in favorable early cases, it seems well warranted in borderline and advanced clinical cases in which conservative methods have little to offer the patient.

SUMMARY AND CONCLUSIONS

Attention is called to the necessity of delivering a larger dose of external radiation to the parametrium if any advance is to be made in the cure of cervical carcinoma.

An attempt in this direction is described. The treatment consists in increasing the target skin distance for external irradiation from 50 to 70 cm., using multiple portals (from four to six) and delivering at least 2,000 roentgens to each field within a period of about three weeks.

This method delivers approximately from 3 to 3.2 threshold erythema doses to the cervix and somewhat less to the parametrium if four portals are used and slightly more if six portals are employed.

Serial biopsies have been studied throughout the course of treatment by roentgen irradiation. The histologic process of regression has been followed, and comparisons have been made between the histologic changes and the degree of clinical regression.

The percentage of satisfactory clinical regressions parallels the increase in the doses. The histologic regressions tend to parallel the clinical regressions. Exceptions are noted.

The lesions are classified into groups based on their gross anatomic character. Polypoid lesions show the greatest clinical regression with external irradiation. Crateriform lesions appear the least susceptible. The latter usually constitute a more advanced clinical type of disease.

Local cure from external irradiation is exceptional with the doses used. By cure is meant complete anatomic disappearance of disease as evidenced by repeated normal results from biopsies over a period of time. One or two normal results are not evidence of cure. Complete temporary epithelization of the primary lesion is not uncommon.

Despite successive biopsies showing progressive degeneration of the tumor and occasionally complete disappearance of disease in one or more specimens examined at the end of the period of external irradiation, the tumor tends almost inevitably to reappear in a histologic form which is apt to resemble closely the initial tumor. Hence restraint of growth is but a transient phenomenon.

For this reason we have little hope that the methods described will control more than a minor percentage of tumors with parametrial extensions. There is a wide gap between the dose delivered to the parametrium by roentgen irradiation (about 3.2 threshold erythema doses) and the 6 to 8 threshold erythema doses necessary for the cure of primary cervical cancer in its usual form. It is thought, however, that the dose to the parametrium may be increased somewhat.

LONGITUDINAL GROWTH OF LONG BONES

J. DEWEY BISGARD, M.D.
AND
M. E. BISGARD, B.A.
OMAHA

Knowledge of the growth of long bones had its beginning with the observations of Stephen Hales [1] in 1747. He drilled two holes in the shaft of the tibia of a growing chicken, and when he examined the bone two months later he found that although the shaft had increased 1 inch in length, the distance between the two holes had remained the same. He also observed that most of this length had been gained at the proximal end. He concluded that growth in the length of long bones is accomplished entirely by deposition of new bone at the extremities and that the amount of growth from the two ends is unequal. These observations have been confirmed by similar experiments of many investigators, among them Hunter,[2] Duhamel,[3] Ollier,[4] Wegner,[5] Humphry,[6] Payton,[7] Kölliker,[8] Haas [9] and Gatewood and Mullen.[10]

Clinical evidence of unequal growth from the two ends of long bones was noted first by Ollier.[4] He observed that children matured with great shortening of a leg in which the knee joint had been resected

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From the Department of Clinical Research, University of Nebraska, School of Medicine.

1. Hales, Stephen: Statical Essays: Vol. 1. Vegetable Staticks, London, W. Innys & others, 1727, p. 337.

Which date?

2. Hunter, J.: Collected Works, London, James F. Palmer, 1837, vol. 4.

3. Duhamel, H. L.: Cinquième mémoire sur les os, Mém. de l'Acad. roy d. sc., 1743, p. 111.

4. Ollier, L. X. E. L.: Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux, Paris, V. Masson et fils, 1867, vol. 1.

5. Wegner, G.: Normal and Pathological Growth of Tubular Bones, Virchows Arch. f. Path. Anat. **61**:44, 1874.

6. Humphry, G. M.: Observations on the Growth of the Long Bones, Med.-Chir. Tr., London **44**:117, 1861.

7. Payton, C. G.: The Growth in the Length of Bones of Madder-Fed Pigs, J. Anat. **66**:414, 1931.

8. Kölliker, A.: Die normale Resorption des Knochengewebes und ihre Bedeutung für die Entstehung der typischen Knochenforme, Leipzig, F. C. W. Vogel, 1873.

9. Haas, S. L.: Interstitial Growth in Growing Long Bones, Arch. Surg. **12**:887 (April) 1926.

10. Gatewood and Mullen, B. P.: Experimental Observation on the Growth of Long Bones, Arch. Surg. **15**:215 (Sept.) 1927.

but with only slight shortening of an arm in which the elbow joint had been removed. He calculated that two thirds of the growth of the leg takes place from the ends of the bones which form the knee joint (the distal end of the femur and the proximal ends of the tibia and fibula) whereas in the arm, only one fifth of the growth occurs at the ends which form the elbow joint.

The first complete and definitive measurements of the quantity of growth which takes place from each end of each principal long bone appeared in 1915. Digby [11] ingeniously reasoned that the nutrient vessels around which long bones begin their formation maintain their original positions at the center of the medullary canals as growth progresses. Thus by projecting the nutrient canal (which always traverses the bone obliquely) until it intersects the center of the medullary canal, the point from which growth started is determined, and growth from each end is measured from this point.

To determine the accuracy of this method of measuring growth and to obtain actual measurements of growth from each end of the principal long bones, the experimental studies herein recorded were carried out.

EXPERIMENTS

New-born goats were used for the experiments so that records of the entire postnatal period of growth could be obtained. Goats were used because they are hardy and survive extensive operations performed during the first few days of life and because they have a substantially large range of growth.

To measure growth the bones were marked with steel shots placed in drill holes in the shafts when the animals were from 2 to 5 days old. All operations were performed with rigid aseptic technic and with the animal under ether anesthesia.

Roentgenograms were taken of the bones at the beginning, throughout the course and at the end of the experiments, which extended over the period of major growth (from twelve to eighteen months). All examinations were made with the extremities in direct contact with the films and with a precisely constant technic.

Final measurements from which growth calculations were made were obtained by actual measurement of postmortem specimens.

EXPERIMENT 1.—*No Interstitial Growth.*

Since the animals used in this study were new-born and were therefore much younger than those used by Wegner,[5] by Gatewood and Mullen [10] and by others, it seemed necessary to repeat their experiments to preclude the possibility of interstitial longitudinal growth of the shaft during early postnatal life.

In twin goats 4 days old shots were placed at measured distances along the entire shaft of a long bone, the humerus in one animal and the radius in the other. Roentgenograms of these bones taken at monthly intervals for the first five months and at postmortem examination twelve months after operation showed that the distances between the shots had constantly remained unchanged. In the postmortem specimens the shots were exposed by grinding away the bone which had been deposited over them, and from actual measurements it was found that the shots

11. Digby, K. H.: The Measurement of Diaphyseal Growth in Proximal and Distal Directions, J. Anat. & Physiol. **50**:187, 1915.

were the same distances apart as when originally placed, thus confirming the observations of the investigators referred to previously. Normally all postnatal longitudinal growth of long bones is accomplished by the addition of new bone at the diaphyseal extremities; there is no interstitial growth in length (fig. 1).

EXPERIMENT 2.—*Measurements of Longitudinal Growth.*

To determine by actual measurements the proportion of growth which takes place at each end of each principal long bone, shots were placed at a measured distance (from 2 to 6 mm.) from the epiphyseal cartilages at each end of the shaft in goats from 2 to 5 days old. Roentgenographic records were made monthly for

Fig. 1.—Right humerus of a goat at the ages of 4 and 358 days. Shots which were placed in the shaft at measured intervals remained equidistant as the bone lengthened. All growth occurred at the ends, principally the proximal end.

five months and then bimonthly until the animals were killed, from sixteen to eighteen months after operation. Representative serial records are reproduced in figure 2. In the postmortem specimens the shots were exposed and exact measurements were made of the distance between the shot and the end of the diaphysis at each end. The difference between these measurements and those recorded at the beginning of the experiment represents the distance that the epiphyseal lines had moved during growth away from the shots, which remained as fixed points to mark the original location of the epiphyseal lines.

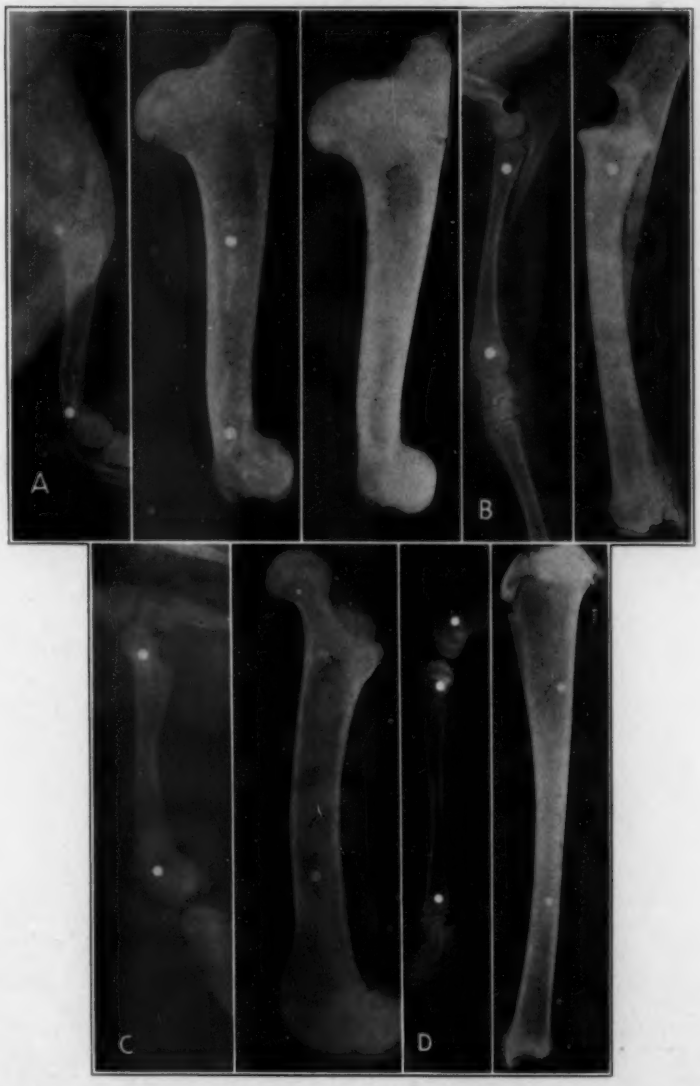

Fig. 2.—A record of postnatal longitudinal growth from the ends of each principal long bone of goats. The ends of the diaphyses were marked with shots placed in drill holes in the cortex when animals were new-born. *A* shows the growth of the right humerus from the age of 2 to 480 days. Both humeri at maturity are pictured to show that they are equal in length and that operative interference in the right one did not disturb normal growth. *B* shows the growth of the right radius at the ages of 4 and 468 days; *C*, of the right femur at the ages of 2 and 480 days; *D*, of the right tibia at the ages of 3 and 472 days. A record of the ulna is shown in figure 5. Note that all growth in all bones has occurred at the ends. The shots have remained the same distance apart.

In five bones the shots did not maintain fixed positions, as indicated by failure to remain the same distance apart throughout the growth. Apparently in each instance the shot at one end had been placed too centrally and had migrated within the medullary canal.

Of the remaining specimens, measurements were made of the humerus in four goats, of the radius in three, of the ulna in four, of the femur in three and of the tibia in three. The goat has no fibula. The measurements were converted into percentages, and the percentages were averaged. In no instance did the proportions of growth for the same bone in three or more animals vary more than 4 per cent.

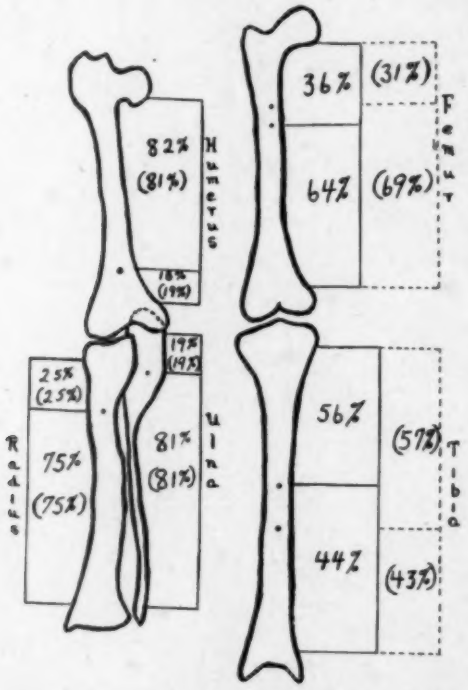

Fig. 3.—The percentages of proportionate longitudinal growth from each end of each principal long bone of a goat are charted as measured from experiments illustrated in figure 2. For comparison, the percentages for total growth for the same bones in man, as recorded by Digby, are included in parenthesis.

The average percentages for each bone are illustrated in figure 3 and the average actual measurements and percentages were as follows:

Bone	Number of Animals Used in Each Experiment	Average Growth, Mm.		Average Proportion of Growth, per Cent	
		Proximal End	Distal End	Proximal End	Distal End
Humerus	4	51	11	82.0	18.0
Radius	3	11	32	25.5	74.5
Ulna	4	20	72	18.8	81.2
Femur	3	29	52	35.8	64.2
Tibia	3	64	53	54.8	45.2

The accuracy of these measurements was affirmed by two control factors: 1. The shots remained the same distance apart throughout growth. 2. The total length of each bone was compared with the total length of its intact fellow on the opposite side. In no instance did these measurements vary more than 5 mm.; in four they were the same, and in thirteen there was a slight overgrowth of the bone subjected to operation. Obviously, neither the operation nor the presence of the shots near the epiphyseal lines had an appreciable influence on growth (fig. 2*A*).

Fig. 4.—From left to right are the humerus, femur and radius of a goat 16 months old, illustrating the method used by Digby for determining percentages of growth. If one assumes that growth began at the point where the nutrient canal intersects the center of the medullary canal, the distance from this point to each end of the diaphysis represents the proportion of growth which has taken place at each end. For purposes of illustration pins have been inserted into the nutrient canals. As illustrated in the radius, the proportions of total growth determined by this method are the same as those of postnatal growth measured from the shots (table 1).

EXPERIMENT 3.—*Evaluation of Method of Digby.*

With accurate percentages of proportionate postnatal growth by controlled actual measurements, an evaluation of the method used by Digby to measure growth becomes a simple procedure.

Both the bones operated on and those used as controls (not operated on) were split longitudinally through the nutrient foramen. Each foramen was projected to a point where it intersected the center of the medullary canal. Measurements from this point to the end of each diaphysis were made. These measurements were converted into percentages, and the percentages were averaged. The principle involved in the method is illustrated in figure 4.

TABLE 1.—*Proportions of Growth in Percentage*

		Femur		Tibia		Humerus		Radius		Ulna	
Period of Growth	Epiphyseal Lines to	Proximal	Distal	Proximal	Distal	Proximal	Distal	Proximal	Distal	Proximal	Distal
I Prenatal	Phosphorus lines	38	62	49	51	83	17	24	76		
(New-born goats)	Nutrient canal (Digby)	42.7	57.3	42	58	60	40	30.4	69.6	33.3	66.6
II Postnatal (goats)	Shots	35.8	64.2	54.8	45.2	82	18	25.5	74.5	18.8	84.2
III Total Goat	Nutrient canal (Digby)	32.7	67.3	56	44	81.7	18.3	25.5	74.5	19.6	80.4
Human*		31.2	68.8	57.1	42.9	80.8	19.2	25	75	18.6	81.4

* These figures are quoted from Digby.

TABLE 2.—*Growth of the Ulna of Goat 18 Over a Period of Sixteen Months* *

	Quantity of Growth					
	Proximal End			Distal End		
	Distance from Shots to Epiphyseal Line, Mm.	Net Growth		Distance from Shots to Epiphyseal Line, Mm.	Net Growth	
Age of Goat		Increase in Mm.	Proportion in per Cent		Increase in Mm.	Proportion in per Cent
4 days	3	..	..	7	..	..
32 days	6	3	23	17	10	77
60 days	8	2	23	24	7	77
90 days	10	2	23	31	7	77
118 days	12	2	25	37	6	75
148 days	13	1	25	40	3	75
180 days	14	1	25	43	3	75
Total						
First six months		11			36	
490 days	20	6	14	82	39	86

* Shots were placed in the ends of the ulna when the goat was 4 days old, 3 mm. from the proximal and 7 mm. from the distal epiphyseal line.

By comparison these percentages are almost identical with those obtained by actual measurements in experiment 2. Philogenetically it is of interest that the proportions of growth from each end of each long bone of the goat differ but slightly from those obtained by Digby [11] for adult human bones. For comparison these percentages have been compiled in table 1 and in figure 3.

EXPERIMENT 4.—*Rate of Growth.*

Humphrey [6] in 1861 observed that the epiphyseal cartilage at the end of the bone from which lesser growth takes place ossifies and closes earlier than the cartilage which contributes major growth. The latter cartilage Payton [7] constantly

found to be thicker. These observations were confirmed in this investigation and are well illustrated in figures 2 *B* and *D* and in figure 5.

In a study of longitudinal growth in madder-fed pigs Payton [7] observed that the rate of growth diminishes (1) as the period of growth advances and (2) more rapidly at the end which has the lesser increment. Our investigation bears out the first contention but not the second. We demonstrated that the relative proportion of growth from the two ends of a bone remains constant until the epiphyseal line which gives lesser growth begins to close. The results are illustrated in figure 5 and in table 2.

In analyzing table 2, it is apparent that growth from both ends was most active during the first four months of life and progressed at almost the same rate during this period. Growth from the distal end then suddenly became retarded to half its previous rate and continued at the new rate until the experiment was terminated.

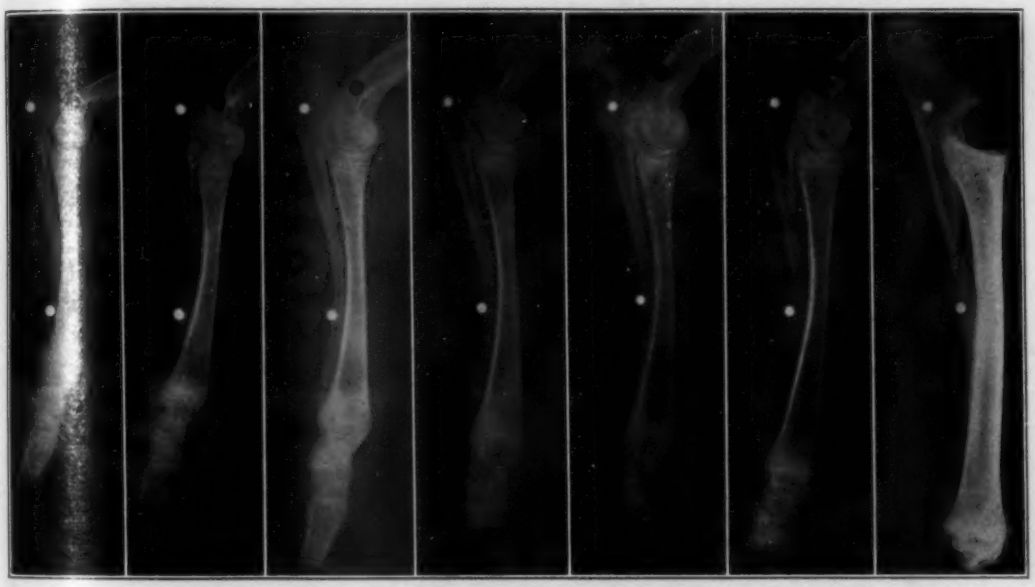

Fig. 5.—A series representing a progressive record of growth of the ulna of a goat, beginning with the third day after birth. The first five roentgenograms were taken at monthly intervals, the sixth at the seventh month, and the seventh at autopsy sixteen months after birth. Note that the rate of growth was rapid and constant for the first four months. It then slowed progressively with advancing age. The ratio between the two ends remained constant for six months.

Growth from the proximal end, however, showed a retardation as the cartilage began to ossify. The ratio of growth from the two ends for the first six months was constantly 3 : 1 (distal end, 75 per cent; proximal end, 25 per cent) and by the end of the subsequent ten months, 5 : 1. It will be noted also that the total growth from the two ends during the first six months was greater than that occurring during the subsequent ten months.

In general, the foregoing findings are applicable to all bones studied. The ulna, and the ulna in this particular goat (goat 18), was selected for illustration only because the series of roentgenographic records of it was technically superior for this purpose.

EXPERIMENT 5.—*Prenatal Growth.*

The investigation thus far has been concerned only with the longitudinal growth which occurs after birth. In order to make similar studies of prenatal growth it was necessary to find a method for marking the embryonic bones as soon after the beginning of ossification as possible. This was accomplished by producing phosphorus growth arrest lines.

Harris [12] has shown that starvation, severe and debilitating diseases, rickets and other nutritional and metabolic disturbances and chemical poisons frequently cause a temporary arrest of growth of bone. During this period the newly formed bone at each end and the adjacent cartilage become densely ossified, and when normal growth is resumed this layer of compact bone persists and casts in the roentgenogram a transverse line marking the site where growth had been temporarily arrested.

Fig. 6.—Principal long bones of a new-born goat, showing growth arrest lines produced by the feeding of phosphorus to the mother at the onset of pregnancy. The nutrient canals have been outlined with pins. The bones from left to right are: ulna, radius, humerus, tibia and femur. As illustrated in the tibia, prenatal growth measured both directly from the growth arrest lines and from the center of ossification shows that growth progresses more nearly equally from the two ends before than after birth.

As has been frequently noted following the original observation of Wegner,[5] feeding of phosphorus provides one of the most effective means of producing growth arrest lines. This suggested the plan of feeding phosphorus to pregnant animals in the hope that it would traverse the placenta and mark the bones of the fetus.

12. Harris, H. A.: Lines of Arrested Growth in the Long Bones in Childhood, Brit. J. Radiol. **4**:561, 1931.

Three ewes were fed 1/25 grain of phosphorus (0.0026 Gm.) daily for six weeks beginning with the onset of pregnancy. One miscarried early, and each of the others delivered twins at term. Roentgenograms taken on the day following birth demonstrated two or more growth arrest lines at each end of each long bone in all four animals. Unfortunately, a line was not laid down early enough to mark the beginning of ossification. Considerable growth had taken place before the first one appeared. In order to obtain accurate measurements and to correlate these with measurements determined by the method of Digby, two were killed, and roentgenograms were made with nutrient canals outlined with pins (fig. 6). The measurements were converted into percentages, and the percentages were averaged. These are recorded in table 1.

The other two animals were reexamined a month after birth, and no vestige of the growth arrest lines remained. These lines, as pointed out by Harris,[12] may disappear promptly in very young, actively growing bone.

Fig. 7.—Principal long bones of a normal new-born goat. From left to right the bones are humerus, radius, ulna, femur and tibia. Note that prenatal growth is more equally proportioned between the two ends and also that the radius and femur each have two nutrient canals and that these intersect each other and the center of the medullary canal at the same point.

The results of this experiment showed that prenatal as well as postnatal longitudinal growth takes place at the two ends and that growth from the two ends is proportionately more nearly equal before than after birth and more nearly equal during the first portion of prenatal life. Except in the tibia, the distances from the center of primary ossification (determined by the method of Digby) to the first growth arrest lines were more equal than the distances from these lines to the epiphyseal lines. Thus, the ratios from the two ends for growth occurring after the appearance of the first lines more nearly equaled those of postnatal growth. It should be noted also that in bones provided with two nutrient canals these canals meet each other at a common point of intersection at the center of the medullary canal. This Digby interpreted as further evidence that ossification starts at the point where the nutrient canal intersects the center of the medullary canal.

In figure 7 are shown the bones of a normal new-born goat. A comparison of the measurements with those of the marked bones shows that the temporary arrest of growth produced by feeding of phosphorus to the mother did not alter the normal ratio of growth from the ends of the bones.

CONCLUSIONS

From the experimental evidence presented it is concluded that in goats:

1. All longitudinal growth of long bones, both prenatal and postnatal, takes places at the ends. Length is gained from the deposition of layers of new bone between the end of the diaphysis and the epiphyseal cartilage and between the articular cartilage and the epiphysis.

2. The proportion of longitudinal growth from the two ends of a long bone is unequal. The disproportion is greater for growth occurring after birth.

3. The rate of growth remains constant during the first four months, and then progresses at half its former rate. The epiphyseal cartilage, giving lesser increment, is the first to ossify and close.

4. The proportion of growth from each end of each long bone, as determined by actual measurements, is recorded. When converted into percentages these proportions are almost identical to those obtained by the method of Digby. We deduce, therefore, that the measurements of proportionate growth for human long bones as determined by Digby are accurate.

5. Growth arrest lines can be produced in the bones of a fetus by feeding phosphorus to the mother.

A CLEAN INTESTINAL ANASTOMOSIS

II. AN EXPERIMENTAL STUDY

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The great variety of technics that have been described and used for anastomosing bowel may seem to exclude the possibility of adding any further suggestions of merit. The very fact, however, that widely different methods can exist and have firm and prominent adherents implies that either there can be no superior procedure or it has not yet been presented. Eminent surgeons do not even agree as to whether the open or the closed form of operation should be adopted in performing entero-enterostomy in the large bowel. There seems to be a sort of fetishism among the more recently trained men requiring the use of the clean or closed method, while many of the best surgeons of the older school insist that better results follow the use of an open technic which permits accurate approximation of tissues without an undue "turn-in" forming a bulky cuff.

An analysis of these two basic methods reveals individual characteristics and fundamental differences. The closed technic tends to minimize soiling and infection but either fails to give good approximation or produces a considerable amount of traumatized tissue as a cuff, which subsequently becomes edematous and causes a temporary postoperative obstruction. This distention of swollen, friable bowel results in an uncontrollable amount of tension on the suture line which may prove disastrous. Frequently hemostasis is questionable. The open method affords the most accurate approximation of tissues with a minimum amount of inversion and cuff. No traumatized tissue need be inverted, and thus postoperative edema, distention, undue tension on sutures and obstruction are minimal. Varying amounts of soiling occur, and when segments of large bowel are sutured this may be considerable. Most patients are able to overcome a considerable amount of infection, but practically all patients with a temporary obstruction have stormy postoperative courses, and leaky suture lines result in abscesses, fistulas, or

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peritonitis and death. Were it possible to combine the good and eliminate the bad features of each method, a more acceptable procedure would present itself.

A closed technic which minimizes soiling, eliminates the inversion of traumatized tissue, allows accurate approximation, insures good hemostasis, permits the use of either silk or catgut for continuous or for interrupted sutures and is rapidly executed without demanding unusual dexterity will be outlined.

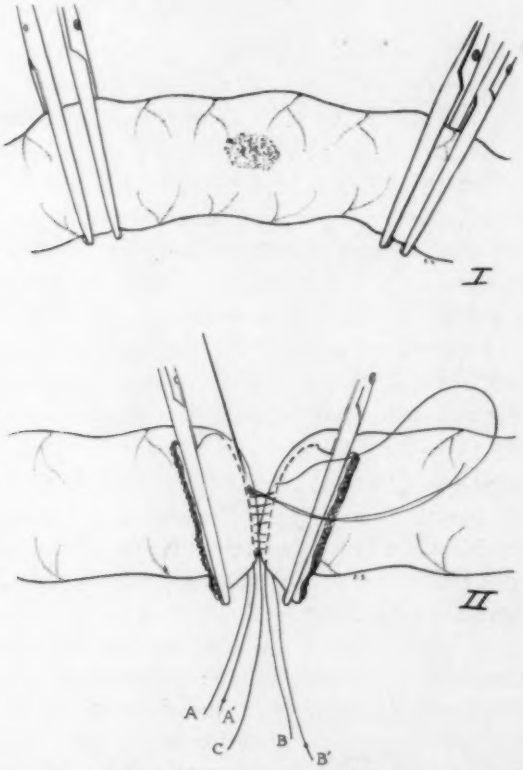

Fig. 1.—Antimesenteric views. *I* shows the clamps placed transversely across the bowel and perpendicularly to the mesenteric-antimesenteric diameter. *II* depicts the stage at which a segment of bowel has been removed, temporary purse-string sutures, *AA'* and *BB'*, are in place and a continuous posterior row is being laid down. Limbs *A'* and *B'* of the two purse-strings are marked with knots near their ends in order that they may be differentiated from *A* and *B* after the sutures are drawn up.

TECHNICAL PROCEDURE

The procedure is readily seen from the successive diagrams when supplemented by a few details. After the segment to be resected has been freed, crushing clamps are applied transversely, at right angles to the mesenteric-antimesenteric diameter, about 1.5 cm. from the chosen line of section. To obviate soiling by

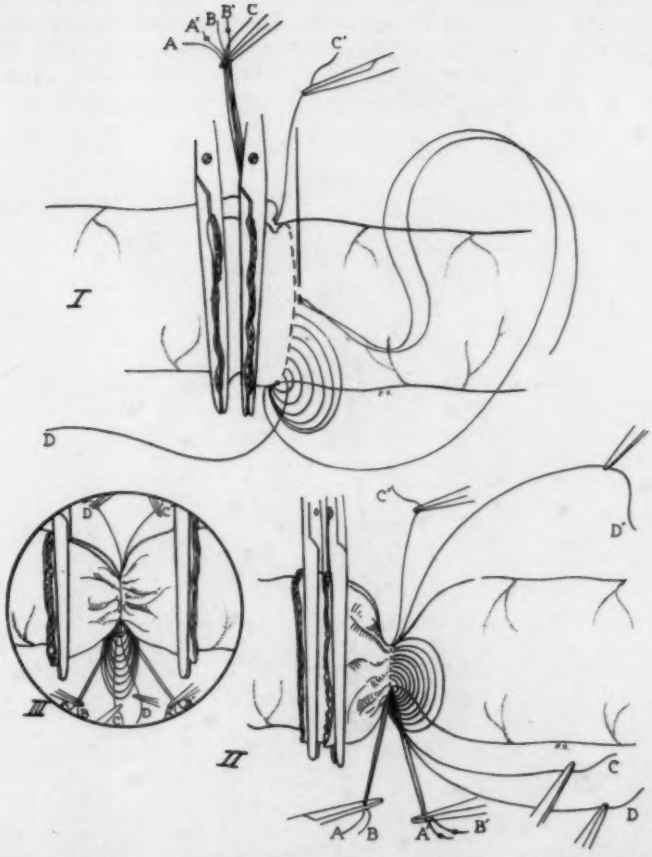

Fig. 2.—Antimesenteric views. *I* illustrates the situation after the posterior row has been pulled tight and both ends of the suture tied without constricting the lumen of the bowel, and a continuous anterior row of sutures is being placed. It is impossible to show the stitches in each segment of bowel. However, the row in the apposing segment is identical with the one shown in the figure. Sutures *A*, *A'*, *B*, *B'* and *C* have been laid across the bowel, on the posterior row of sutures, and between the two occluding clamps so as not to interfere with the placing of the anterior row. *II* shows the anterior suture, *DD'*, applied. While in actual practice the loops of the anterior suture are drawn snugly against the edges of the bowel, they are made long in the drawings to insure clear illustration. Neither end of this suture is tied. The purse-strings, *AA'* and *BB'*, are pulled up so as to close the bowel. Only one knot has been placed in each of the purse-strings so that they will pull up smoothly. They are not tied. *III* illustrates the appearance after the two occluding clamps have been separated to reveal the region of the inner posterior suture after the purse-strings have been drawn up.

forcing organisms through the wall of the crushed bowel, the serrated jaws of the clamps are treated with liquid phenol. This treatment is permissible since the tissues involved will be removed subsequently. The viscus is divided between the clamps, and the cut ends are cauterized with heat or phenol. Two purse-strings, (*AA'* and *BB'*, fig. 1) are placed at the levels selected for anastomosis, which should be about 1.5 cm. from the occluding clamps. This makes it possible to close the ends of the bowel later by drawing up these sutures before removing the clamps. However if it is inconvenient to sacrifice this additional length of bowel the purses-strings may be placed as near the clamps as desired. Deknatel surgical silk [1] no. 2 is the best material for these temporary sutures.

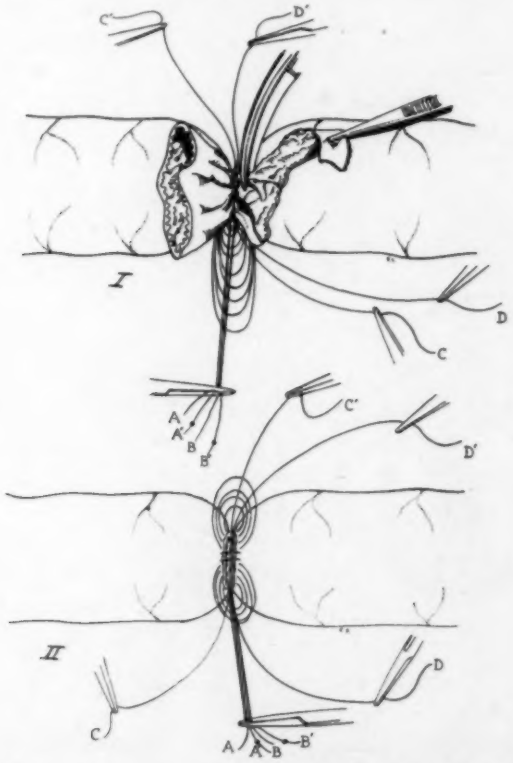

Fig. 3.—Antimesenteric views. *I* shows the stage at which the clamps have been removed successively, the mucous surfaces have been treated with liquid phenol, and the excess cuff is being trimmed off with scissors to about 2 mm. beyond the temporary purse-strings. Bleeding vessels are clamped and tied as they are encountered. *II* illustrates the stage at which the ends of the sutures *A, A', B, B'* and *C* are carried underneath the loops of the anterior row and the anterior suture, *DD'*, is pulled up beginning at its middle.

The inner posterior row of sutures (*C* in fig. 1, II) are placed close against the purse-strings. These sutures may be continuous or interrupted, and either silk

1. This silk may be obtained from J. A. Deknatel and Sons, Inc., Queens Village, L. I., N. Y.

or catgut may be used. The sutures are tied at once since the bowel is not constricted and the proper amount of tension can be applied. After the sutures (*AA'*, *BB'* and *C*, fig. 2) are laid across the bowel on the posterior row and between the two occluding intestinal clamps the inner anterior line of sutures is placed. Either silk or catgut may be used, but whatever material is selected is best employed as a continuous suture. The loops of the suture between the successive stitches, which are taken so as to include a few fibers of submucosa, are carried around the edge of the bowel and under the ends of the clamps. If silk is used it is imperative that Deknatel surgical silk no. 1 or no. 2 be employed, because that silk is a hard, strong braided thread which slips through tissues

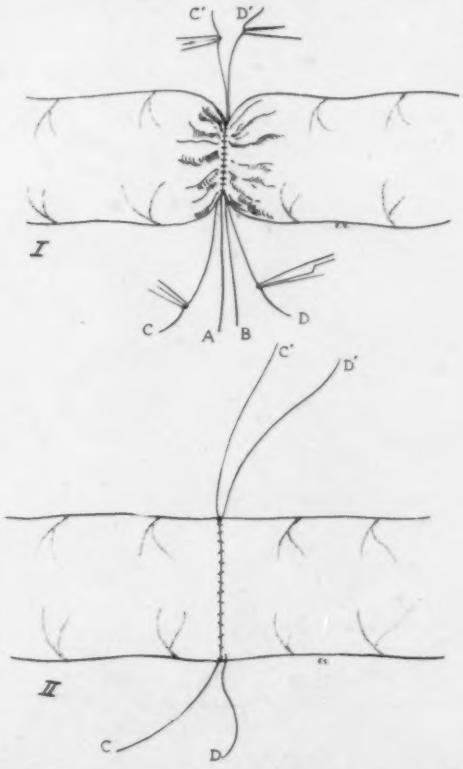

Fig. 4.—Antimesenteric views. *I* shows the stage at which the suture, *DD'*, of the anterior run has been pulled up, and one limb, *A'* and *B'*, of each purse-string has been cut short; *II*, the stage at which the temporary purse-strings have been withdrawn and the bowel has been opened out to its full diameter.

readily and does not fray. Since the diameter of the bowel is not constricted, it is possible to place all the sutures accurately even though the segments to be joined have different cross-sections.

After a single knot has been tied in each purse-string, the purse-strings are drawn up simultaneously to occlude the lumen of the viscus but not sufficiently tightly to interfere with free bleeding from the cut ends. The purse-strings must be pulled up simultaneously so as not to damage the posterior row of sutures. The intestinal clamps are removed successively, and the mucosal surface of each

cuff is treated thoroughly with liquid phenol. The cuff is trimmed to within approximately 2 mm. of the tightened purse-strings. This is easily accomplished, and care must be taken not to trim the edges too closely. Bleeding vessels are clamped and tied as they are encountered (fig. 3*I*). When it proves necessary to place the purse-strings close to the clamps the contents of the bowel are milked back and restrained with digital pressure or rubber-shod intestinal clamps while the crushing clamps are removed and the purse-string sutures are pulled up. The purse-strings are not tied, except with a single knot, but this need cause no anxiety, as they show no tendency to loosen. The ends of the sutures *A*, *A'*, *B*, *B'*

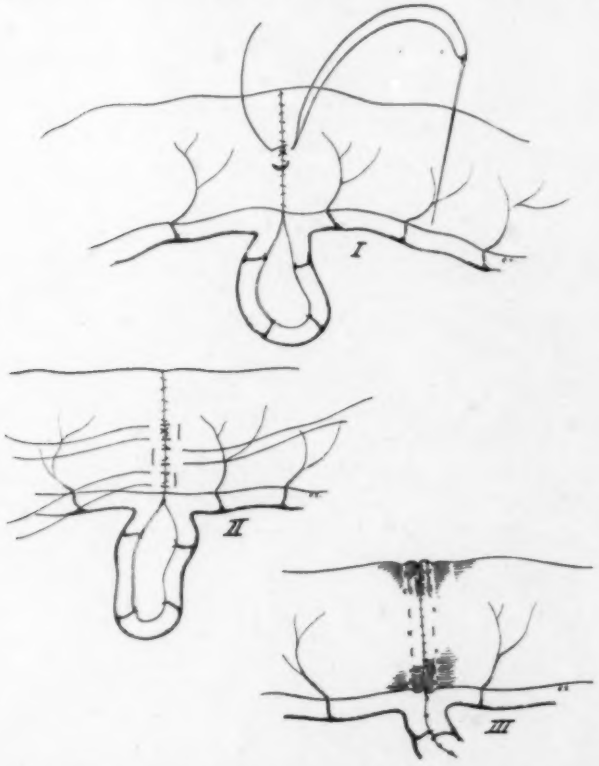

Fig. 5.—Side views. *I* shows the stage at which the anterior row is being tied so as to cover the knot of the posterior suture. Each end of the anterior row is secured in this manner. *II* shows the stage at which a second row of sutures is being placed, and *III*, the completed operation.

and *C*, are passed underneath the loops of the anterior suture *DD'* and the anterior row is pulled up, beginning at the middle as indicated in figure 3*II*. Then one limb of each purse-string is cut short and the balance of the purse-strings withdrawn. The bowel is opened out to its normal diameter by gentle traction on *CC'* and manipulation of the constricted tissue (fig. 4*I* and fig. 4*II*). After each end of the anterior suture has been rethreaded, a stitch is taken so as to tie this suture and cover the knots of the posterior row. This completes the inner row. Any type of suture can be selected as a second, reenforcing row (fig. 5).

COMMENT

Obviously this procedure is the logical conclusion to a technic previously suggested by me.[2] While most of the underlying principles are the same as in the previous procedure, a simplified and more readily executed method of operation is presented. No traumatized tissue is turned in to form a massive cuff, which would become edematous and result in a temporary obstruction, stormy postoperative course and protracted convalescence. The amount of tissue inverted is under the complete control of the operator, since not more that 2 mm. of bowel need to extend beyond the inner row. Accurate approximation of corresponding portions of viscus is realized because all the anastomosing

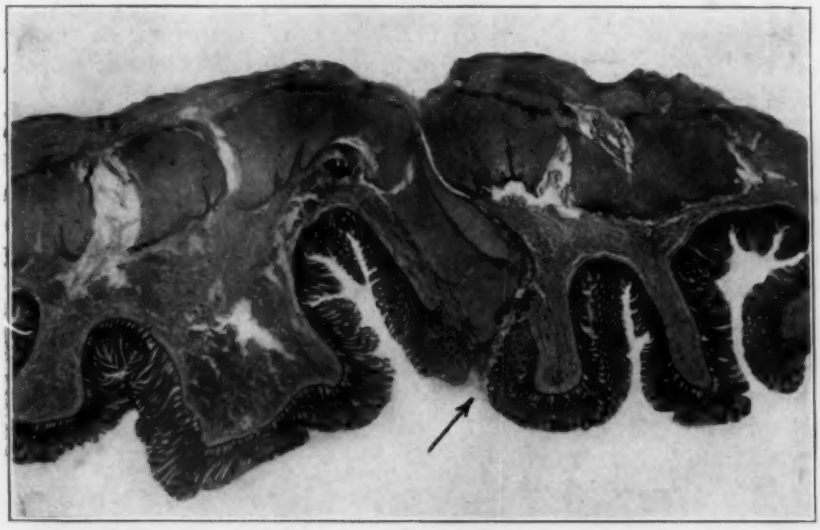

Fig. 6.—Photomicrograph (× 10) of a segment of the large bowel showing the relationship and accurate approximation of tissues immediately after the first row of sutures has been placed.

sutures are placed in nonconstricted sections of bowel. After the inner row of sutures is in place and the purse-strings are withdrawn the submucosa at the cut edge tends to retract and bring the opposing mucosal edges into close approximation. This completely covers the line of anastomosis on the side of the lumen with mucosa. The mucosal flaps form a perfect check valve against leakage into the peritoneal cavity and at the same time establish free drainage of the inner line of sutures into the lumen of the bowel (fig. 6). Bleeding is controlled by direct ligation of the vessels when the excess of cuff is cut away.

2. Poth, Edgar J.: A Clean Intestinal Anastomosis, Arch. Surg. **28**:1087 (June) 1934.

Since the lumen of the intestine is occluded by the purse-strings before the clamps are removed, soiling is reduced to a controllable minimum. Moreover, the purse-strings are simple devices which do not demand dextrous manipulations.

A large series of these operations have been performed on dogs in anastomosing segments of both large and small bowel; either silk or catgut or both have been used as continuous or as interrupted sutures, and end-to-end, side-to-side and end-to-side anastomoses have been established. All the animals have been followed closely over a period of months, and exploratory laparotomies have been performed from time to time. There have been no deaths due to peritonitis or obstruction. No stitch abscesses have occurred, and few adhesions have been found even in animals having three end-to-end sutures performed at the same sitting within a 5 inch (12.7 cm.) segment of the descending colon and sigmoid. Five months after operation no obvious or palpable thickening or constriction of the bowel has been found.

While almost any type of sutures desired may be employed, the following materials are preferable: (1) Deknatel surgical silk no. 2 for the purse-strings, (2) 00 chromic catgut on a swedged needle as a continuous suture for both the anterior and the posterior portion of the inner row and (3) fine black silk placed as a Halsted mattress stitch for a second row of anastomosing sutures.

THE PENDULOUS HYPERTROPHIC BREAST

COMPARATIVE VALUES OF PRESENT-DAY METHODS OF REPAIR AND THE PROCEDURE OF CHOICE

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NEW YORK

The pendulous hypertrophic breast occurs far more often than is generally realized. It is frequent in young girls as well as in women who have borne children and may occasion great physical and mental distress. As a whole the medical profession has not taken cognizance of the prevalence or attendant discomforts of this condition, and many physicians are unaware that safe and successful methods of repair are available. It is my purpose briefly to classify and describe the etiology of the pendulous hypertrophic breast, to compare the principal surgical methods that are employed to correct this deformity and to present an operation in two stages that I consider the procedure of choice.

CLASSIFICATION

It must be made clear at the outset that by the term hypertrophy is designated not only true hyperplasia of the mammary gland, which is rare, but various other forms of overdevelopment. In all there are four main types of hypertrophy of the breast: (*a*) true hypertrophy, which is rare; (*b*) fatty hypertrophy, the most common type; (*c*) hypertrophy as a result of mastitis (nodules and cystic fibroma), also a frequent variety, and (*d*) congenital relative hypertrophy, in which one breast is larger than the other.

It is extremely important to distinguish between the true hypertrophied breast and the ordinary oversized fatty breast, as the treatment and prognosis of the two conditions differ radically. True hypertrophy is characterized by a marked increase in the glandular structure and only a slight augmentation of fatty tissue. Most authors consider the true hypertrophied breast of puberty the characteristic type. The enlargement starts inconspicuously between the ages of 14 and 16 and then develops rapidly, reaching the climax within a few months. The breast attains enormous proportions, often extending below the umbilicus and to the pubis, and there are frequently concomitant disturbances in the general health.

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To this type may be added another form of true hypertrophy which occasionally appears during pregnancy. This variety is rarer than the true hypertrophy of puberty, but it has similar clinical manifestations. It differs from the first type chiefly in its time of onset and in the fact that it is likely to diminish spontaneously after childbirth.

Far more common than true hypertrophy is hypertrophy with fatty degeneration, which often has no relation to generalized adiposis. In this condition the breasts become enlarged at an early age and gradually increase, their augmented weight producing ptosis. Fatty tissue, which is present throughout the breast, predominates in the lower portion, especially in the external quadrant. Glandular tissue is scarce and is usually seen at the bottom of the ptosed breast sac (fig. 1).

Another type of hypertrophy of the breast which is often seen is that caused by mastitis. In these cases the breast is invaded by multiple nodules (cystic fibroma or fibro-adenoma), varying in size and number.

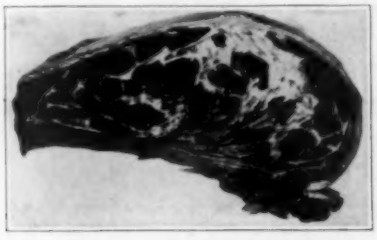

Fig. 1.—Section taken from a hypertrophic breast. The light parts represent glandular structures; the dark, fatty tissue (from Joseph).

Frequently in this form of hypertrophy the breasts are asymmetrical, owing to an unequal development of the mastitis. In one of my cases in which the condition was due to this cause, the left breast was about one-third larger than the right (fig. 7).

Among the congenital types of hypertrophy the only abnormality common enough to warrant comment is mammary asymmetry. Needless to say, I am not speaking of minor diversities in size which are present in the breasts of virtually every woman. I am concerned here only with the cases of marked asymmetry, in which one breast is conspicuously enlarged. Usually these malformations are associated with other anatomic abnormalities of the thoracic wall or of the extremities. Two of my patients showed definite thoracic maldevelopment on the side of the larger breast.[1]

1. Maliniak, J. W.: Asymmetrical Breast Deformities, Ann. Surg. **99**:743 (May) 1934.

ETIOLOGY

True hypertrophy of the breast is a pathologic manifestation the cause of which is not yet known.

In fatty hypertrophy there is undoubtedly a strong hereditary factor. Enlarged, pendulous breasts are frequently observed in several successive generations.

That there is an endocrine contribution also seems likely. The relationship between the mammary glands and the ovaries is indisputable; the physiologic and anatomic changes occurring in the breast at puberty are strongly influenced by hormones of internal secretion. It seems highly probable that an excess of these hormones accelerates the development of the breast.

Hypertrophy which is the result of mastitis is, of course, due to the factors responsible for the mastitis. The underlying cause is often trauma of some kind, such as repeated lactation or pressure from tight brassières.

There is considerable evidence in support of the theory that prenatal maldevelopment is an important etiologic factor in the production of asymmetry of the breast. While associated malformations are not, as a rule, present in cases of the common varieties, extreme types usually present accompanying abnormalities.[1]

The mechanism of ptosis is easily understood. Mammary prolapse is a natural phenomenon in woman, occurring as the weight of the breast increases and its supporting structures become distended. A rapid increase in the volume and weight of the breast hastens the natural tendency to prolapse; the base of the breast is shifted downward, and the skin and suspensory ligaments are stretched. Pregnancy and lactation accentuate these factors.

Lack of proper support is another important element. False modesty often constrains girls at puberty to suppress their normally developing breasts by tight brassières, or, as in the postwar period, fashion may decree a boyishly flat chest, the semblance of which can be achieved only by a compressive bandeau. At the same time that the bandeau flattens the breasts it pulls them downward, stretching the skin and suspensory ligaments. It is natural that girls should seek to conceal abnormally large breasts, but the tight brassières which they use to achieve this purpose merely increase the ptosis. A proper support raises the breasts to their normal position but of course displays their proportions. In almost all my cases there was a history of early sensitiveness and the use of restrictive brassières to conceal the overdeveloped breasts.

CONSIDERATIONS OF SURGICAL TREATMENT

Indications for Surgical Intervention.—Naturally not all large breasts should be submitted indiscriminately to surgical treatment, and the oper-

ative indications should be carefully considered in each case. The following factors are of prime importance in reaching a decision: the degree of deformity; the age of the patient and her attitude toward the malformation; the influence of the abnormality on systemic health, and the extent to which it interferes with normal social and economic life.

Although fatty hypertrophy cannot be considered a pathologic manifestation, it may indirectly exercise an adverse effect on the general health. Traction on the muscles and skin of the shoulders and thoracic region causes pain and produces faulty posture. The heavy breasts make activity difficult; the women become sedentary in their habits, and adiposity and general sluggishness result. Because of excessive perspiration and disturbed circulation, dermatitis develops in the submammary region. This condition demands continual care, particularly in warm weather. The presence of these distressing conditions is a warrant for surgical treatment.

Alleged Contraindications.—For some reason the question of plastic repair of the breast is rarely discussed in medical literature, and when it is considered the result is more likely to be confusion than clarification. As a consequence, hypertrophy of the breast often appears to be misunderstood, and fallacious arguments are advanced against surgical procedure for relief of the condition, which do not stand the test of searching analysis.

The first charge that is brought against operative reconstruction of the breasts is disturbance of mammary function. It is true that most breasts do not lactate after plastic repair, but, on the other hand, the pendulous hypertrophic mamma per se is rarely capable of lactation. Surgical treatment, therefore, cannot be held responsible for the absence of function in this kind of breast.

The question of conspicuous scarring has also been raised, but this too has no validity as a deterrent to surgical treatment. In the procedure of choice, which will be described later in this paper, the principal scar is placed in the submammary fold.

These considerations do not, of course, enter into the surgical treatment of true hypertrophy. In this condition amputation affords the only hope of relief. An attempt to simulate the normal appearance of the chest can be made in these cases by a free graft of the nipple and areola from the amputated breast.[2] The surgical principle is less drastic and more hopeful in the correction of other types of hypertrophy.

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2. Dartigues, L.: De la greffe autoplastique libre aréolo-mamelonnaire, combinée à la mammectomie bilatérale totale: Les raisons de sa prise, Paris chir. **2**:11 (Jan.) 1929.

Requirements for Successful Repair.—To constitute an acceptable method of repair, the procedure for the correction of a pendulous hypertrophic breast should embrace the following concepts:

1. The blood supply of the breast must be preserved in order to prevent partial necrosis.

2. Extensive injury to the galactophorous ducts should be avoided in order to preserve partial mammary function when possible.

3. The gland must be firmly affixed in its new location to prevent recurrence.

4. There should be no conspicuous scarring.

5. All the diameters of the breast must be reduced proportionately to insure an esthetic end-result.

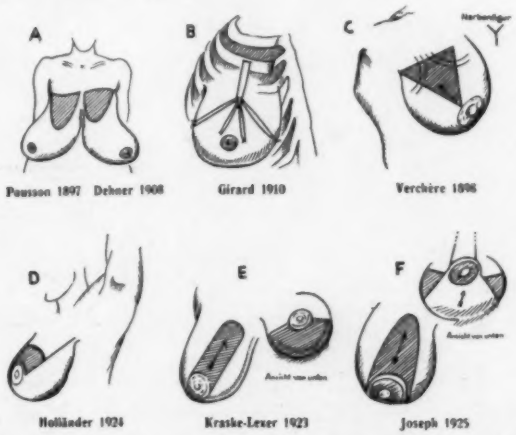

Fig. 2.—Diagrams showing procedures for the plastic repair of the hypertrophic breast now rarely used. Diagrams *A*, *C* and *D* show the enlarged breast raised, following excision of the skin by various procedures; *B* shows the disk-shaped excision of glandular tissue through the submammary fold and the affixation of the gland to the rib and fascia, and *E* and *F* illustrate the open transposition of the areola to a higher location with and without a pedicle. These procedures, originated by Lexer and Kraske and by Joseph, are still in use with some modifications.

These critera must be borne in mind in the evaluation of the various surgical procedures which I am about to describe.

COMPARISON OF SURGICAL METHODS

Without regard to the numerous modifications that have been made, there are two main procedures for the correction of the pendulous hypertrophic breast: the method of transposing the nipple through a buttonhole incision and the method of open transposition. Proper evaluation of these procedures necessitates the consideration of the evolution of each of these methods (fig. 2).

In 1909 Morestin described before the French Academy of Medicine the plastic repair of hypertrophic breasts by the removal, through an incision made in the submammary fold, of a disk-shaped segment from the posterior aspect of the gland.[3] This procedure was apparently applied to overdeveloped, protruding breasts which had to be flattened. He made no mention in this communication of the use of a buttonhole incision for transposition of the nipple; but Villandre,[4] referring in 1925 to a patient on whom he had operated in 1911, gave Morestin credit for the procedure.

In 1910 Girard,[5] in a communication before the International Congress of Surgery in Berlin, presented a method of plastic repair similar to that of Morestin and of Dehner;[6] he removed excessive fat and glandular tissue through an incision in the submammary fold and affixed the upper pole of the gland to the rib. Lotsch[7] in 1923 published a procedure similar to that attributed to Morestin; he transposed the nipple to a higher position but made an additional vertical incision in the midline. This modification had the disadvantage of leaving a conspicuous scar on the lower pole of the breast, but it made possible a more accurate adjustment of the excessive skin.

In 1925 Passot[8] and Dufourmentel,[9] pupils of Morestin, published a procedure for the plastic repair of the breast by transposition of the nipple through a buttonhole incision. Reduction and transposition of the mamma were done in a single operation. Axhausen[10] reported a similar method in 1926.

The procedures described by Kraske[11] and by Joseph[12] in 1923 and 1925, respectively, were based on open transposition of the nipple to a higher location after excision of an oblong fragment of skin. Joseph left a cutaneous bridge attached to the areola to insure its blood supply. Lexer made a circular incision around the areola, transposing it upward,

3. Morestin: Hypertrophie mammaire unilatérale corrigée par la résection discoïde, Bull. et mém. Soc. d. chirurgiens de Paris **35**:996 (Oct. 20) 1909.

4. Villandre, cited by Dartigues, L.: Arch. franco-belges de chir. **28**:325, 1925.

5. Girard, C.: Mastoptose und Mastopexie, Verhandl. d. deutsch. Gesellsch. f. Chir. **39**:200, 1910.

6. Dehner: Mastopexie zur Beseitigung der Hängebrust, München. med. Wchnschr. **55**:1878, 1908.

7. Lotsch, Fritz: Ueber Hängebrustplastik, Berl. Gesellsch. f. Chir., May 14, 1923; abstr., Zentralbl. f. Chir. **50**:1241, 1923.

8. Passot, R.: La correction esthétique du prolapsus mammaire par le procédé de la transposition du mamelon, Presse méd. **33**:317, 1925.

9. Dufourmentel, L.: Bull. et mém. Soc. d. chirurgiens de Paris **17**:219, 1925.

10. Axhausen, G.: Ueber Mammaplastik, Med. Klin. **22**:976, 1926.

11. Kraske, H.: Operation der atrophischen und hypertrophischen Hängebrust, München. med. Wchnschr. **70**:672, 1923.

12. Joseph, J. Zur Operation der hypertrophischen Hängebrust, Deutsche med. Wchnschr. **51**:1103, 1925.

and removed the excessive fat and glandular tissue principally from the lower pole (fig. 2). Biesenberger[13] reduced the breast to one-half its original size by removing the external half of the gland and rotating upward the lower end of the inner half. It is unnecessary to mention other methods which have been suggested. The principal ones have already been outlined and furnish sufficient material for consideration before discussing the procedure of choice. The German methods may first be considered.

Method of Joseph.—To the least critical eye it is apparent that the method of Joseph is unnecessarily complicated and inflicts much needless scarring. By merely excising the skin above the nipple and

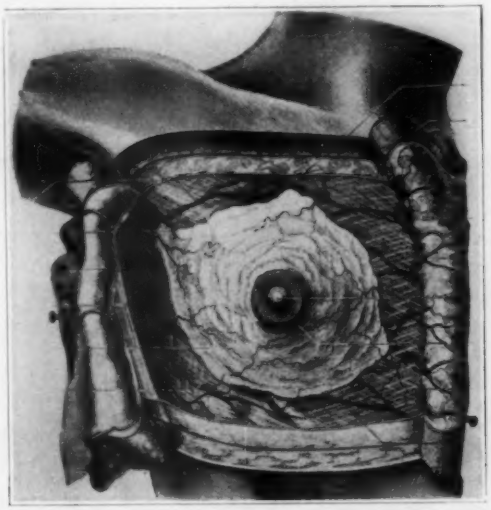

Fig. 3.—Drawing showing the main blood supply of the glands of the breast provided by the thoracic lateral and internal mammary arteries (from Testut). The blood supply must be preserved during transposition of the areola in the procedure of choice.

shifting the latter structure to a higher position, he obtained a purely cutaneous suspension of the central portion of the gland without affixation to the deeper structures. Ideal modeling of the breast in all diameters is impossible, and there is strong likelihood of recurrence of ptosis. Joseph's use of a cutaneous bridge proceeded from his belief that the circular incision around the areola interferes with the blood supply of the nipple and may cause necrosis. This, however, has not been the experience of the majority of surgeons using the circular incision, for the nipple derives its principal blood supply from the thoracic and the

13. Biesenberger, cited by Joseph.[14]

internal mammary artery, and no sloughing occurs if these channels are preserved (fig. 3).

Joseph later modified his method and adopted an operation in two stages.[14] In the first stage, instead of transposing the nipple openly, he transferred the areola subcutaneously on a pedicle into a resected window (fig. 4). The pedicle was detached from the transposed nipple in a second operation. Aside from the fact that this method invites infection by leaving skin in contact with a raw surface, it is an unnecessary precaution since the nipple derives its main blood supply not from the skin but from the interior blood vessels.

Method of Lexer and Kraske (fig. 2).—Since in this procedure the excess of fat and glandular tissue is removed by a vertical crescentic excision from the lower pole of the breast, extending from the nipple to the submammary fold, the closure of the resulting defect causes the breast to protrude conspicuously. The suspension of the gland is purely cutaneous, thus producing a predisposition to recurrence of the

Fig. 4.—In diagrams *A* and *B* is shown the modified procedure of Joseph in which the diminished areola is transposed on a pedicle in a buttonhole under a small cutaneous bridge (*a*, *b*, *c* and *d*). In *C*, after complete healing the lower half of the areola is shown detached from the pedicle and sutured to the upper border (*a-b* of *B*) of the cutaneous bridge. The hypertrophic parts of the breast are excised, and the lower border of the bridge (*c-d* of *B*) is sutured in the submammary fold.

ptosis. The end-result is further subject to criticism from the esthetic standpoint because of the impossibility of modeling the breast accurately in all diameters.

Method of Biesenberger (fig. 5).—The method of Biesenberger, which reduces the breast by the excision of its external half, ingenious as it is, appears to be attended by certain risks. Since suppression of an important part of the blood supply may produce necrosis, it seems somewhat risky to abolish the thoracic lateral artery and depend solely on the internal mammary artery for the vitality of the areola and the remaining tissue of the breast. In addition, to my mind,

14. Joseph, J.: Nasenplastik und sonstige Gesichtplastik nebst Mammaplastik, Leipzig, Curt Kabitzsch, 1930, vol. 3, p. 791.

torsion of the pedicle is an unwelcome possibility in the rotation of the lower pole of the inner half of the gland around the center. Apparently this procedure is safe in the hands of its author, but the potential danger of necrosis looms large in my mind.

Procedure by a Buttonhole Incision.—The procedure by buttonhole incision, originated by Morestin and Villandre and subsequently adopted with modifications by Dufourmentel,[9] Dartigues,[15] Passot [8] and myself,[16] is free from most of the objections that can be raised against other methods. A large flap is made on the anterior aspect of the breast, and all the skin is removed from the posterior surface, permitting reduction and modeling the breast in all diameters. The nipple and areola are inserted into a buttonhole incision in the anterior flap, and the gland, around which a circular incision has been made, is firmly affixed to the pectoral fascia, preventing recurrence of ptosis. Scarring is minimized by suturing the flap into the submammary fold (fig. 6). When this

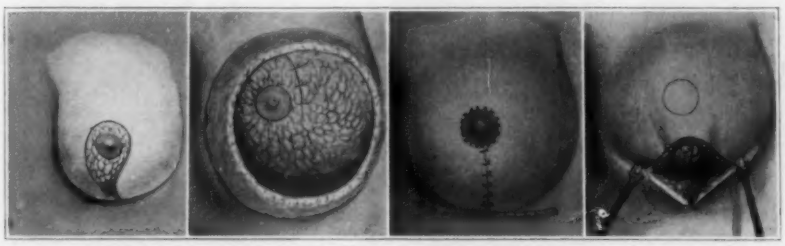

Fig. 5.—Drawing showing the steps in the procedure of Biesenberger in which the extreme half of the breast is excised and the lower pole of the remaining half is turned upward to produce a spherical shape. According to the author, the two breasts are reconstructed in one stage.

operation is performed in one stage, as it originally was done by the followers of Morestin, there is no doubt that the danger of necrosis is present. I myself had peripheral necrosis of the skin in several of my first patients, sometimes only along the line of suture but in one case over an extensive area below the nipple, between the buttonhole and the submammary fold, in which the blood supply is not of the best and the tension is greatest (fig. 6). Tension, it may be said, is one of the chief factors in this complication. In two cases in which the breasts were large and pendulous but without much fat, necrosis

15. Dartigues, L.: Traitement du prolapsus mammaire, Arch. franco-belges de chir. **28**:313 (April) 1925.

16. Maliniak, J.: Pendulous Breast: Etiological Factors and Surgical Treatment, Comptes rendus de la Congrès de la Société française de chirurgie réparatrice, plastique et esthétique, Paris, Norbert Maloine, 1931.

of the nipple occurred on one side. This was due to the removal of much glandular tissue, especially in the external quadrant, necessitating ligation of some of the branches of the thoracic lateral artery.

Preservation of the blood supply is of the utmost importance in the prevention of necrosis, and discoloration of the nipple is a warning which should not be disregarded (fig. 3). In two of my patients the transposed nipple promptly became cyanotic, and normal color did not return even after prolonged application of heat, as often happens if the blood supply has been preserved. If discoloration is the product of tension, this should be immediately relieved.

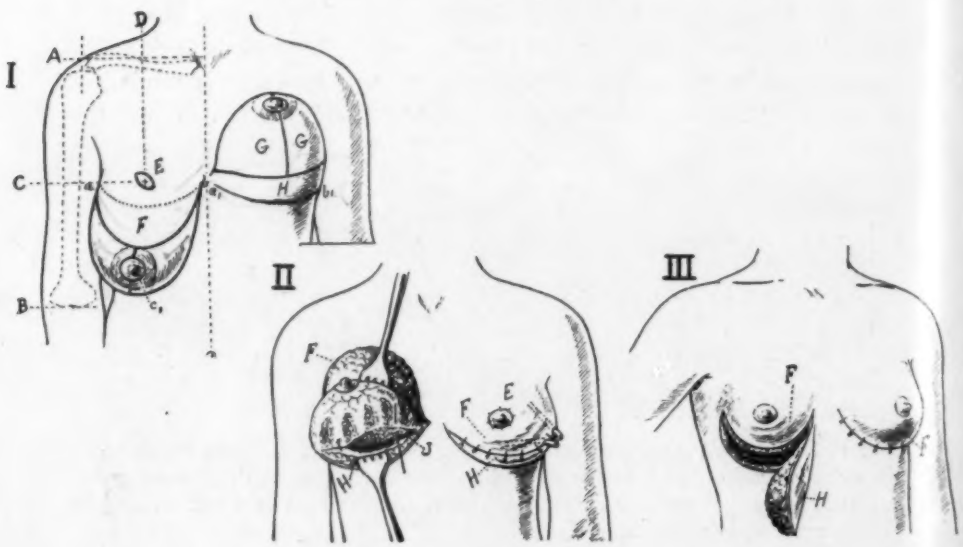

Fig. 6.—Diagrams illustrating the procedure of choice—the two stage method—for the repair of a hypertrophic breast. In diagram *I* horizontal lines are drawn (*A*) across the clavicle, (*B*) through the elbow joint and (*C*) half-way between *A* and *B;* a vertical line (*D*) is drawn through the middle point of the clavicle. Point *E*, the intersection of *C* and *D*, determines the new location of the nipple. *F* represents the anterior flap extending to the areola; *G*, the excessive skin around the areola; *H*, the flap of skin on the posterior aspect of the breast to be sutured to flap *F*, and *a-b*, the submammary fold. The flaps are outlined to bring about the covering of the reduced breast without tension. The areola is transposed and sutured into a buttonhole (*E*) made in the anterior flap (*F*). The incision on the posterior aspect of the breast is made above the submammary fold (*a-b*), outlining a flap (*H*) to be sutured to flap *F*. In diagram *II* are shown the closure of the defect in the right breast and the appearance of the left breast after transposition of the areola and suturing of the flaps of skin. In diagram *III* are shown the removal of excessive skin, fat and glandular tissue by a crescent-shaped excision along the submammary fold (right breast) and the final condition after closure of the defect (left breast).

If only the skin is necrosed, the damage is not as great as when necrosis of the nipple occurs. In the former contingency the defect is epidermized after sloughing has taken place, and the resultant scar can be easily eradicated. When the nipple sloughs, it cannot be replaced.

Torsion of the pedicle is another important cause of necrosis. It can be avoided by taking suitable precautions against rotating the pedicle as the nipple and gland are transposed.

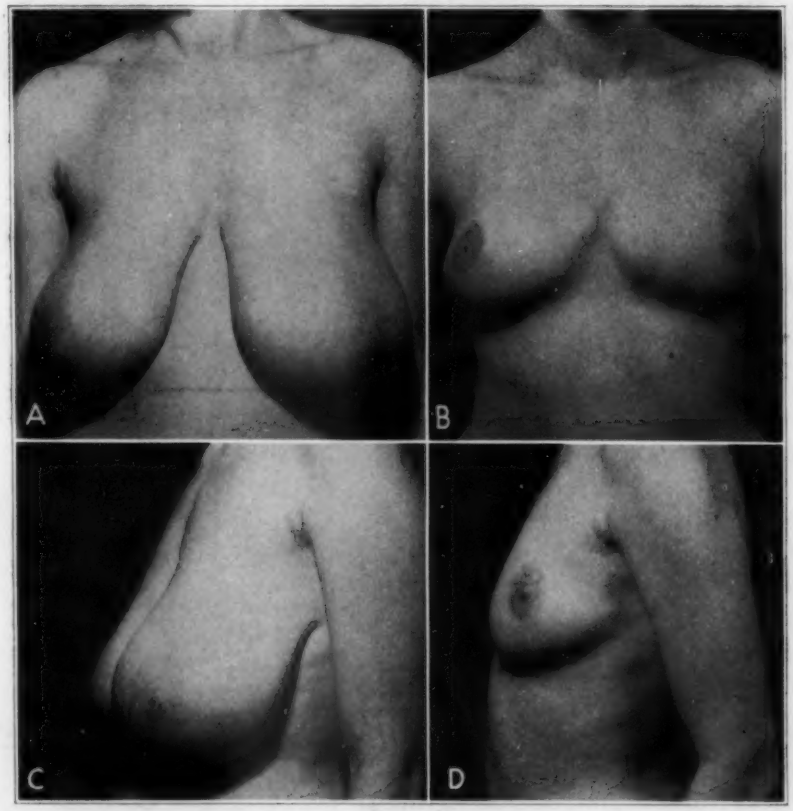

Fig. 7.—In *A* and *C* is shown hypertrophy of the breasts in a case of bilateral cystic mastitis occurring in a girl of 23. Both breasts were considerably oversized at the age of 16 and became particularly enlarged and painful at the age of 22. Unbearable physical discomfort rendered reconstruction urgent. In *B* and *D* is shown the appearance following plastic repair done in two stages.

Method of Choice.—The few early cases of necrosis which I have described prompted me to abandon the one stage procedure in favor of a method which would preserve the blood supply as completely as possible and avoid tension during transposition of the areola. The two stage operation which I am now using as the method of choice has

satisfactorily solved the problem for me. Since its adoption I have never had the slightest sign of necrosis of the skin or nipple in any of my cases.[17]

The first stage of the repair is limited to transposition of the partially diminished breast (fig. 6). A circular incision is made around the

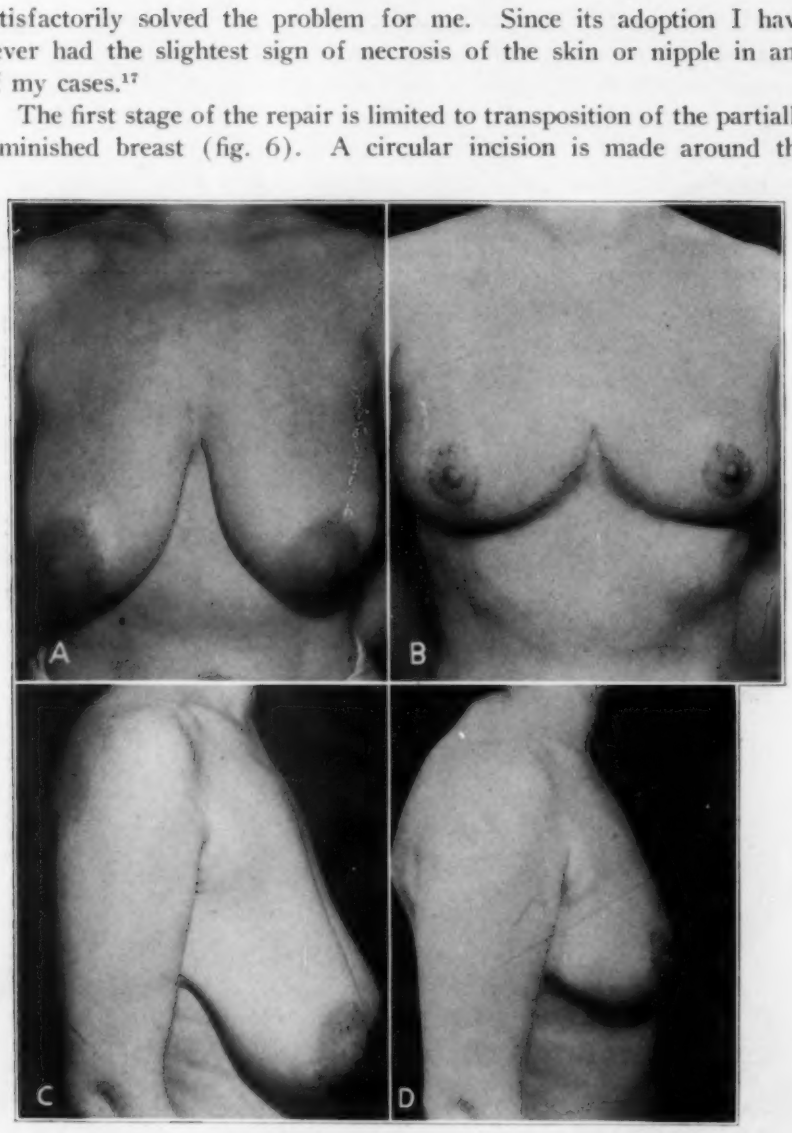

Fig. 8.—*A* and *C* show the hypertrophic and pendulous breasts occurring in a married woman of 28 which greatly interfered with her profession as pianist. Repair was done by the two stage procedure. In *B* and *D* is shown the final result a few weeks after the second stage of the operation.

areola, reducing it to the normal size. A concave incision on the anterior aspect of the breast reaches from one side of the submammary fold

17. Maliniak, J.: The Pendulous Hypertrophic Breast, Am. J. Surg., to be published; footnote 1.

to the other. A flap is separated, extending as high as the second intercostal space, and a buttonhole incision is made into which the areola is sutured. In most cases the upper pole of the breast is affixed to the pectoral fascia before suturing of the areola. The skin is removed from the posterior surface of the breast to an extent determined in each case by the size of the transposed organ, the chief consideration being the avoidance of tension on the lines of suture. Hematoma is prevented by drainage of the undermined area through the external angle of the incision. There is no disturbance of the blood supply in the external quadrant. If reduction of the gland is performed at the first operation, it is limited to the lower pole. The branches of the internal mammary artery on the inner side of the breast are usually left undisturbed.

In thirty breasts corrected in this way, not once did cyanosis of the nipple or necrosis of the skin occur. The color of the nipple was gratifyingly reassuring immediately after transposition, in striking contrast to that in my experience with the one stage operation.

The second stage is carried out from four to six weeks later, when the nipple has completely "taken" in its new location. The excess skin, fat and glandular tissue are removed through a crescent-shaped excision in the submammary fold.

When correction is bilateral, this procedure does not lengthen the surgical period. In the one stage operation the correction is usually done separately on each breast, thus requiring two surgical periods for completion. If one performs the first stage of the operation on each breast at the same time, as I do, the repair on the two breasts is finished together, and the total time required for reconstruction is the same as with the one stage method (figs. 7 and 8).

SUMMARY AND CONCLUSIONS

1. The pendulous hypertrophic breast is more common than is generally believed, in young girls as well as in women, and occasions both mental and physical distress. There are four main types—true hypertrophy, fatty hypertrophy, hypertrophy resulting from mastitis and congenital asymmetry.

2. Among the etiologic factors are embryonic maldevelopment, heredity, endocrine disturbances, repeated pregnancies and periods of lactation and trauma.

3. The suppression of mammary function is not a contraindication for reconstruction, as normal function is rarely present in the pendulous hypertrophic breast.

4. The procedure of choice is a two stage method. The first stage consists of transposition of the partially reduced breast, with preservation of the blood supply and avoidance of tension. Excision of the remaining excessive skin, fat and glandular tissue is done in the second stage after the nipple has "taken."

5. The two stage procedure is a safe method for the correction of a common and distressing deformity. The danger of necrosis is entirely eliminated, and the end-result is assured. There is no conspicuous scarring, since the main scar is concealed in the submammary fold.

1125 Park Avenue.

MULTIPLE MENINGIOMAS

REPORT OF A CASE IN WHICH THREE INTRACRANIAL MENINGIOMAS WERE REMOVED SUCCESSFULLY

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Meningioma, which constitutes from 10 to 15 per cent [1] of the tumors found within the cranial cavity, usually occurs singly, although the occurrence of multiple intracranial meningiomas is by no means unknown. Hosoi,[2] in 1930, reviewed the literature and reported twenty-two cases of multiple meningiomas, including one of his own (see table).

A case not included in Hosoi's list was reported by von Anfimow [3] in 1889. The patient, a man 36 years old, was found at necropsy to have four large and many small dural endotheliomas. There was no mention made of associated tumors of other types.

In 1932 Üprus [4] reported the finding of ten intracranial meningiomas in a patient who had suffered for fifteen years with headaches and vomiting. List,[5] in 1933, likewise found multiple meningiomas at necropsy in a woman, 53 years old, who had undergone exploratory operation for a cerebellar tumor. Von der Hütten [6] described the case of a woman, aged 30, who had complained for four months of increasing

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From the Section on Neurologic Surgery, the Mayo Clinic.

1. H. W. Cushing (Intracranial Tumors: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C. Thomas, Publisher, 1932) estimated that meningiomas constitute 13.4 per cent of the intracranial tumors. H. W. Cushing and Percival Bailey (Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928) estimated an incidence of 12.22 per cent, and Craig, 14.9 per cent.

2. Hosoi, K.: Meningiomas with Special Reference to Multiple Intracranial Type, Am. J. Path. **6**:245 (May) 1930.

3. von Anfimow, J.: Ein Fall multipler Geschwülste in der Schädelhöhle, Neurol. Centralbl. **8**:585 (Oct.) 1889.

4. Üprus, Voldemar: Meningiomas multiplex cerebri, Folia neuropath. estoniana **12**:86, 1932; abstr., Zentralbl. f. d. ges. Neurol. u. Psychiat. **67**:44, 1933.

5. List, C. F.: Multiple Meningiome der Schädelbasis. (Zugleich ein Beitrag sur Differentialdiagnose der Kleinhirnbrückenwinkeltumoren), Nervenarzt **6**:566 (Nov. 15) 1933.

6. von der Hütten: Beitrag zur Diagnose von Hypophysentumoren, Ztschr. f. Laryng., Rhin., Otol. **24**:95, 1933.

headache and diminishing vision. Her condition was diagnosed as hypophyseal tumor, and she was operated on transnasally according to the Hirsch technic. She died three weeks after operation, and at necropsy twenty-five endotheliomas, situated chiefly at the base of the skull, were found. Frazier and Alpers [7] recently stated that they found only one example of multiple tumors in their series of seventy-five cerebral fibroblastomas.

Cushing [8] collected reports of thirteen cases from the literature and noted the frequent occurrence of multiple meningiomas with tumors of the acoustic nerve and multiple neurofibromatosis. He was of the opinion

Review of the Literature and Report of Twenty-Two Cases of Multiple Meningiomas

Case	Reported by	Age, Years	Sex	Number of Primary Meningeal Tumors	Associated Findings
1	Wishart	21	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
2	Langdon	32	F	Numerous	Unilateral acoustic tumor
3	Henneberg and Koch	26	M	Numerous	Bilateral acoustic tumor
4	Schmidt	77	M	Two	None
5	Schmidt	88	M	Two	None
6	Fraenkel and Hunt	42	M	More than 100	Bilateral acoustic tumors
7	Westphal	26	F	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
8	Verocay	31	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
9	Henschen	25	M	Numerous	None
10	Leischner	40	M	Numerous	Unilateral acoustic tumor
11	Heuer and Dandy	..*	M	Two	None
12	Greenfield	31	M	Three	None
13	Symonds	27	M	Numerous	Bilateral acoustic tumors and multiple neurofibromatosis
14	Krivy	..†	F	Three	None
15	Firket	27	F	Ten	Bilateral acoustic tumors and one spinal meningioma
16	Casper	..†	F	Numerous	None
17	Casper	52	M	Numerous	None
18	Casper	72	F	Numerous	None
19	Savy and others	39	M	Two	None
20	Regnier and others	36	M	Two	Bilateral acoustic tumors and multiple neurofibromatosis
21	Flick	54	F	Numerous	None
22	Hosoi	30	F	Thirty-eight	Multiple angiomas

* The patient in this case was an adult.
† The patients in these cases were old.

that while these might be correlated lesions, they were of utterly different pathologic character.

Hosoi noted that in 50 per cent of the series of cases which he collected multiple meningiomas were not associated with other tumors. This suggested to him that the association of meningeal tumors and multiple neurofibromatosis was an expression of the predisposition of the person to hereditary and dysontogenetic influences.

7. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum: Clinicopathologic Analysis of Seventy-Five Cases, Arch. Neurol. & Psychiat. **21**:935 (May) 1933.

8. Cushing, H. W.: Tumors of the Nervus Acusticus and the Syndrome of Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917.

More recently, Penfield and Young [9] reported the postmortem examination of a patient with multiple tumors in the connective tissue sheaths of nerves, in the meninges and in the central nervous system. The nature of the tumors in each situation was peculiar to the tissue in which they appeared. In addition to the neoplasms, the authors found in each of the three tissues definite evidence of a hyperplastic reaction of the cells peculiar to those tissues. They suggested that a congenital defect in the nervous system is perhaps capable of producing irritation and that this irritation causes hyperplasia of the cells which is followed by a neoplastic change. They were of the opinion that the fact that the cells of the tumors were peculiar to the tissue in which they were found speaks in favor of the production of tumor by an irritative process rather than from embryologic rests.

Much less common than reports of cases of multiple meningiomas are instances of the successful removal of these multiple tumors. Heuer and Dandy,[10] in 1916, reported such a case. The patient had been operated on elsewhere in 1908, at which time a single dural endothelioma, lying in the motor area, was removed. The symptoms recurred, and in 1909 another operation was performed at the Johns Hopkins Hospital; a recurrent tumor was found at the site of the previous operation and a second tumor compressed the motor speech area. A search of the literature reveals this to be the only report extant of the removal of multiple meningiomas at operation; reports of all other cases of multiple tumors were based on observations at necropsy.

The following case, in which three meningiomas were removed, was considered worthy of report:

REPORT OF CASE

A married woman, aged 46, registered at the clinic on April 18, 1934, complaining of pain in the head and in the right arm, which she had had for eight months, and of dimness of vision, which had been present for three months. In September 1930 she had been examined in the clinic, at which time it was found that she had mild hypertension; otherwise, she was in excellent physical condition. The onset of the illness for which she came to the clinic had occurred when, on reaching for a ball which had been thrown, she suddenly experienced a sharp pain in the right side of the thorax. Later an aching pain in the right arm developed, which was projected up to the neck and occiput and over the vertex to the frontal region. At times the pain became so severe that it was necessary to give morphine hypodermically for relief. For three months prior to her admission vision had diminished progressively, and for six weeks ataxia had been developing. She had experienced some dizziness but had had no convulsions or vomiting. Just before admission she had become conscious of weakness in the fingers of her right

9. Penfield, W., and Young, A. W.: The Nature of von Recklinghausen's Disease and the Tumors Associated With It, Arch. Neurol. & Psychiat. **23**:320 (Feb.) 1930.

10. Heuer, G. J., and Dandy, W. E.: A Report of Twenty Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**:224 (Aug.) 1916.

hand. According to her friends, there had been a definite change in personality; at times her mind had seemed flighty and her memory poor.

General examination showed the patient to be slightly obese but in good general condition. Neurologic examination disclosed that she was slightly deaf in each ear. The corneal reflex was diminished bilaterally. The muscles of the right forearm and hand were weaker than the corresponding muscles of the left upper extremity. The Hoffman reflex was present on the right, as were moderate astereognosis and incoordination.

On examination of the eyes, the fields were normal except for enlarged blind-spots. Vision in the left eye was 6/10; in the right eye, 6/20. There were bilateral choked disks of 4 diopters, with a few hemorrhages.

The results of urinalysis and of all examinations of the blood were normal. Roentgenograms of the head gave evidence of a rounded, calcified mass in the left basofrontal region, the shape of which suggested a calcified meningioma (fig. 1).

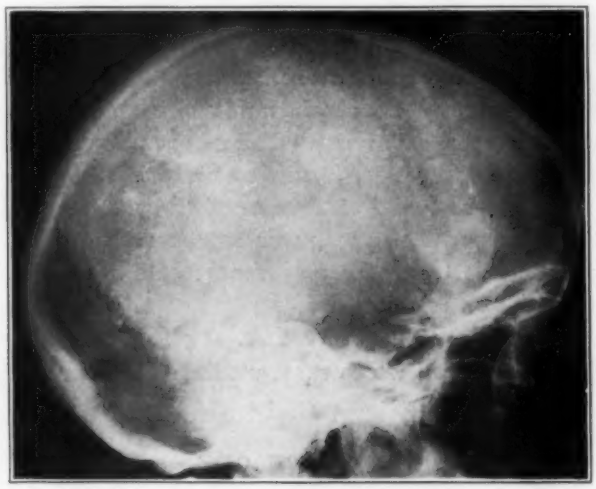

Fig. 1.—Calcified meningioma in the left basofrontal region.

Because of the change in personality, the weakness and incoordination of the right arm, the numbness of the fingers of the right hand, the bilateral choked disks and the roentgenographic finding of a calcified mass in the left basofrontal region, a diagnosis was made of calcified tumor involving the left frontoparietal lobes. It was thought that this tumor probably was a left basofrontal meningioma.

Left transfrontal craniotomy was performed; the opening was made larger than usual because of the questionable nature of the calcified mass. As soon as the dura had been exposed, a meningeal tumor was found compressing the posterior part of the inferior frontal convolution. The tumor was firm and corresponded to the shadow found in the roentgenogram of the head. It was easily rolled from its bed and was found to measure 3 by 2 by 2.5 cm. It was removed with its dural attachment, and when the dura was incised forward a small meningioma, measuring 1 by 1 by 0.5 cm., was found and removed (fig. 2). In view of the fact that these two tumors failed to explain the weakness of the right arm and the high degree of papilledema, further search was made, and another meningioma, which measured 5 by 5 by 3 cm., was found compressing the motor cortex near the arm area. This was removed with a great deal of difficulty on account

of the vascularity of the capsule and the numerous vascular attachments. Although the situation and size of the third meningioma that was removed accounted satisfactorily for the symptoms, the basofrontal region was explored by elevating the left frontal lobe; no evidence of tumor was found. The wound was closed after the cortex had been protected with Cargile's membrane to take the place of the defects in the dura caused by removal of the attachments of the meningiomas.

Pathologically the tumors were all meningiomas, but they varied greatly in gross, as well as in microscopic, appearance. The smallest of them was very soft and friable and contained no calcium. The medium-sized tumor was hard and unyielding because of marked calcification, which had been demonstrated in the roentgenograms. The largest tumor, and the last to be removed, was well encapsulated, contained no calcium and was quite vascular (fig. 3). Microscopically

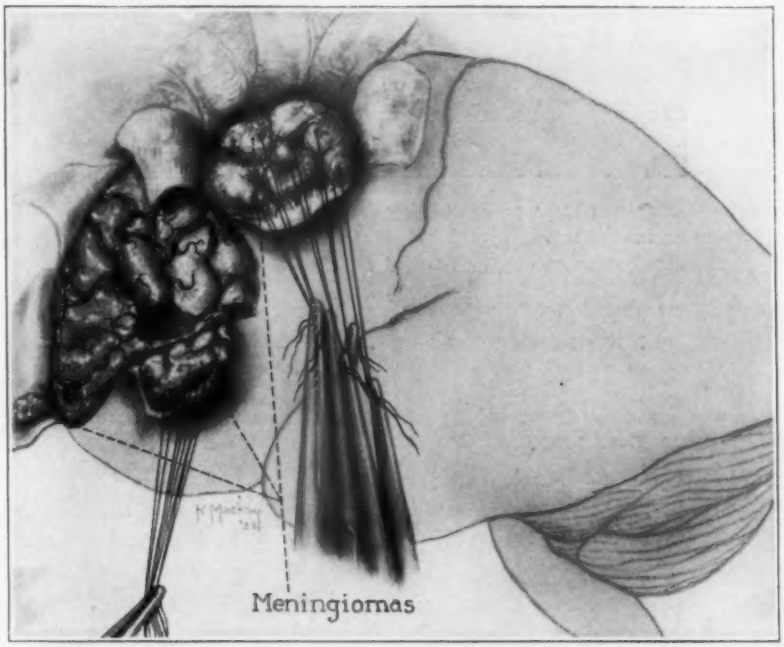

Fig. 2.—The three tumors as they appeared at operation.

it proved to belong, as did the other two, to the meningiomatous group of tumors known as meningiomas, meningeal fibroblastomas or dural endotheliomas.

At the operating table it was difficult to understand why the patient did not have aphasia, in view of the fact that the calcified meningioma compressed Broca's area. Consequently, we were not surprised that the patient became completely aphasic on the second day after the operation and remained so until the sixth day, when she began to improve. Her convalescence was otherwise uneventful. She was dismissed from the hospital on the twelfth day after operation and was allowed to return home on the fifteenth day. At the time of dismissal the papilledema was definitely subsiding, and she had completely recovered from aphasia; there was still, however, some weakness of her right arm (fig. 4).

A letter received from the patient seven months after the operation was written with her right hand, the function of which had been completely restored. She

stated that her general condition was excellent and that her vision was progressively improving.

COMMENT AND SUMMARY

Removal of multiple meningiomas by operation with relief of symptoms is of such rare occurrence that it warrants comment. A review of the literature fails to reveal a similar case, although multiple meningiomas have been reported from observations at necropsy and are

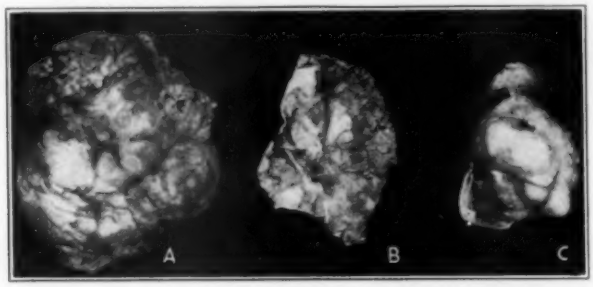

Fig. 3.—Gross specimens of the meningiomas that were removed. The measurements were as follows: *A*, 5 by 5 by 3 cm.; *B*, 1 by 1 by 0.5 cm. (including a piece of the dural attachment), and *C*, 3 by 2 by 2.5 cm.

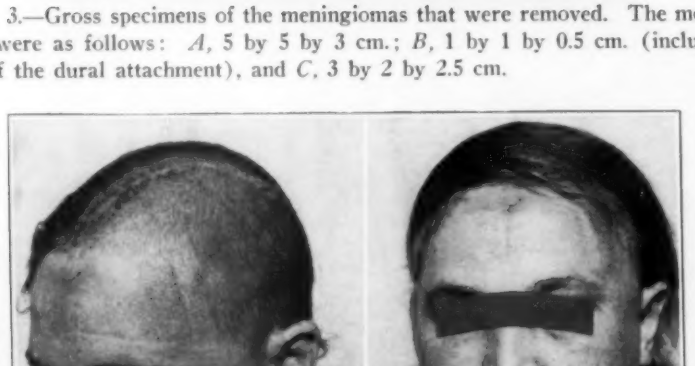

Fig. 4.—The patient sixteen days after operation, showing the well healed incision.

frequently associated with acoustic neuromas or generalized neurofibromatosis. The present case illustrates the difficulty in localizing and determining the pathologic nature of an intracranial lesion prior to surgical exposure. At operation a calcified lesion was found to correspond with the shadow in the roentgenogram, but it was felt that the presence of this tumor did not explain the papilledema or the weakness in the right hand. Further search revealed another tumor, which was responsible for these symptoms.

ACUTE ABDOMINAL PAIN IN SICKLE CELL ANEMIA

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Attacks of acute abdominal pain with fever, muscle spasm and leukocytosis occur not infrequently with sickle cell anemia. The attacks are often severe and may be associated with signs and symptoms strongly suggesting various acute abdominal diseases. In fact, the picture may so closely simulate such a condition as to be almost indistinguishable, even if the patient is known to have sickle cell anemia. Furthermore, persons with sickle cell anemia are just as subject to the other abdominal diseases as any one else, and instances of cholelithiasis, appendicitis and other emergency conditions are well known. Hence, it is important for a surgeon to be familiar with the painful manifestations of sickle cell anemia. It is to enumerate the symptoms and signs most commonly found in this interesting phase of the disease and to report six cases in which the abdominal manifestations were outstanding that this paper is written.

General Description.—(Cook and Meyer [1915]; Josephs, [1928]; Syndenstricker [1920, 1929]; Eastland and Higgins [1930]).—Sickle cell anemia is of the familial hemolytic group (Sydenstricker [1924]) and occurs solely in Negroes [1] or in persons with Negro blood. It is characterized by the peculiar sickle or oat shape which the erythrocytes assume in a fresh preparation. The disease occurs in an active and a latent form (Sydenstricker [1924]; Huck [1923]), and one may succeed the other (Mulherin and Houseal [1924]). In the active phase there may be long periods when the hemolytic process is quiescent, and no signs or symptoms of the disease are present. The sickling trait persists throughout life. Some persons may never have the active form and hence have no anemia or any symptoms of the disease, and the anemia may be discovered only by the study of a preparation of fresh blood. It has been estimated that from 2 to 7.5 per cent (Branbau [1932]; Cooley and Lee [1926]; Sydenstricker [1920]; Miyamoto and Korb [1927]) of the entire Negro population has sickle cell anemia in the latent form, while a much smaller proportion has the active variety.

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1. The possible exceptions to this are the cases described in the reports by Stewart (1927), Archibald (1926), Lawrence (1927), Rosenfeld and Pincus (1932) and Auer (1933).

Patients with active sickle cell anemia usually complain of weakness, dyspnea and general poor health. The symptoms sometimes appear in attacks of a few days' or even months' duration and sometimes are constantly present over longer periods. At intervals the symptoms disappear entirely. There is a tendency for the patient to contract an intercurrent infectious disease. Often there is a history of attacks of malaise, fatigability, fever and jaundice, sometimes associated with abdominal pain and vomiting, sometimes with pain in the joints and long bones. Several instances have been reported in which laparotomy (Levy [1929] and cases 1, 2 and 6 in this paper) or operation for acute osteomyelitis (Dreyfoos [1926]; Alden [1927]; Leivy and Schnabel [1932]) has been carried out with negative results and subsequent discovery of sickle cell anemia. Bronchitis is rather common, and night sweats are not infrequent.

On physical examination one often finds some enlargement of the heart with a systolic apical murmur, moderate general glandular enlargement and a palpable liver. It is probable that in the active form in young children the spleen enlarges until the age of from 3 to 5 years and then gradually becomes smaller (Anderson and Ware [1932]; Ching and Diggs [1933]; Stewart [1927]). In cases of the latent type no gross evidence of splenic changes may be observed at autopsy. In some clinics ulcers of the leg have been reported in many cases, though that has not been my experience. Infantile genitalia have been noted in some of the malnourished patients. Characteristic radial striations in the calvarium are sometimes seen in roentgenograms (Cooley and Lee [1925]; Moore [1929]).

Hematology of the Active Form.—Anemia is usually present. In 49 instances Anderson and Ware (1932) found an average red blood cell count of 3,500,000, a hemoglobin content between 30 and 40 per cent and a leukocyte count of from 10,000 to 12,000. The erythrocyte count may be as low as 600,000 and the hemoglobin content as low as 10 or 12 per cent, while the white blood cell count has been reported in some cases to be above 60,000. During exacerbations in younger persons lymphocytosis is not uncommon (Landon and Lyman [1929]; Bothe [1933]; Hamilton [1926]; Russell and Taylor [1932]). The color index has been reported as from 0.7 to 1.4. Varying degrees of anisocytosis and poikilocytosis are found. In the active phase the erythrocytes assume the sickle shape almost immediately in the preparation of fresh blood. The sickling varies greatly, even in the same patient, in the time when it appears, in the percentage and in the subsequent return of the red blood cells to normal shape (Cooley and Lee [1925]). No relation between the degree of sickling and the severity of the symptoms has been noted. Nucleated red blood cells

and reticulocytes are present in varying percentages. The changes in the platelets are not noteworthy. Hyperbilirubinemia with mild jaundice and increased urobilin in the urine is common. The van den Bergh reaction is usually negative in the direct phase and positive in the indirect. The fragility of the red blood cells is not increased, and it may be slightly diminished. The urine may have low specific gravity.

Pathologic Changes.—The changes most characteristic of this anemia are to be found in the spleen, both in the latent and in the active phase. As described by Rich (1928), they "consist in a congenital malformation of the sinuses of the spleen, which permits the free escape of blood into the pulp." As in congenital hemolytic jaundice, the entire pulp may be filled with blood. "The anomaly characteristic of sickle cell anemia is the pronounced malformation of the sinuses immediately about the malpighian bodies, leading to the formation of pools of blood partially or completely surrounding" these structures and probably caused by imperfections in the ampullae of Thoma. There may be "an abnormal development of capillaries" throughout the malpighian body. "The reticulum of the spleen is not primarily abnormal." Hemosiderin may be demonstrated in the tissues (Graham [1924]; Rich [1928]). The bone marrow is hyperplastic in the active stage.

I am reporting six cases of sickle cell anemia because of the abdominal manifestations.

REPORT OF CASES

CASE 1.—*Priapism four months previously. Epigastric pain, constipation, vomiting, malaise, jaundice, marked distention and leukocytosis. Similar attack three months previously. Diagnosis, probable ileus. Exploratory laparotomy with normal findings. Sickle cell anemia discovered subsequently.*

Winston R., a 14 year old Negro, was admitted to the hospital on Aug. 20, 1932, with a complaint of abdominal pain, obstipation, malaise and jaundice. The attack began about seven days previously, when the jaundice was first noticed and when the constipation commenced. The abdominal pain had varied in degree, had sometimes been severe and had always been located in the epigastrium. The patient had vomited on two or three occasions but had not done so for the past three days. Various cathartics had been taken without effect. It was interesting to note that he had a similar attack of pain, jaundice and constipation three months before, and his mother added that on a number of occasions during the past five years he had "spells" of jaundice lasting for a few days or a few weeks, during which time he would feel badly. Four months previous to examination he had been treated successfully for priapism in the urological dispensary by aspiration of blood clots from the corpus cavernosum.

On examination the temperature was 99.6 F., the pulse rate was 80, the respiratory rate was 18 and the white blood cell count was 30,000. The patient was definitely jaundiced, the skin was dry, there was slight general glandular enlargement and the heart and lungs were normal. The abdomen was markedly distended and rather tense. There was very slight generalized tenderness, perhaps more in the epigastrium and in the right upper quadrant, but there was no

definite muscle spasm. The liver and the spleen were not palpable, nor was any other mass felt. There was no rebound tenderness, and no peristalsis could be seen. An enema was ineffectual, and gastric lavage yielded about 150 cc. of bile-colored fluid.

The etiology of a probable ileus was not clear, and after observing the patient for some hours a laparotomy with appendectomy was done by Dr. H. J. Warthen Jr. The findings were normal throughout. The temperature rose to 101 F., and the pulse rate the day after the operation was as high as 180 and did not fall below 120 for forty-eight hours. The van den Bergh test showed a prompt biphasic reaction and 8 mg. per hundred cubic centimeters. The white blood cell count the next day was 42,000, and it was only then that a fresh blood smear was found to show sickle cells.

The patient was transferred to the medical service, where he remained for about seven weeks. The hemoglobin content was 40 per cent, the red cell count, 2,800,000, polymorphonuclears, 91 per cent, and lymphocytes, 8 per cent. On the second day postoperatively the enemas began to be effectual, and the distention was gradually relieved. The nonprotein nitrogen content was elevated, being 80 mg. on the third postoperative day and 50 mg. on the fifth day. The cholesterol content was 166 mg. per hundred cubic centimeters. The red blood cell count fell to 1,500,000 by the sixth day, and the patient was given a transfusion of blood. On the same day the value for nonprotein nitrogen fell to 32 mg. per hundred cubic centimeters, or normal. It was then found that the liver was palpable 3 fingerbreadths below the costal margin. The spleen and kidneys were not palpable. The hemoglobin content rose to 40 per cent and the red cell count to 2,100,000 after the transfusion. The white cell count was then 16,600. On the eighth day the patient had a good deal of abdominal pain, which was relieved by enemas, and he vomited once. The wound was now healed, and on the twelfth postoperative day the hemoglobin content was up to 45 per cent, the red cell count to 2,500,000 and the reticulocyte count 1.1 per cent. The patient improved slowly and gradually gained weight. The white cell count remained elevated at about 20,000. The nonprotein nitrogen content did not rise again during his stay in the hospital. The gastric analysis with histamine showed free acid of 22 mg. and a combined acid of 20 mg. No ulcers of the leg were present, nor was there any evidence of cardiac enlargement.

The patient was followed in the dispensary from October 13 to July 7, 1933, at which time he was admitted to the hospital because of weakness and cough. His temperature was 101.6 F., and there were jaundice, pallor and signs of bronchopneumonia at the base of each lung. The red cell count was 1,200,000, and on two occasions transfusions of 300 cc. each were given, bringing the red cell count up to 2,400,000. The fever subsided, and the patient was allowed to go home after two weeks in the hospital, feeling much better.

He was readmitted on November 7 for a transfusion of blood. The hemoglobin content was 40 per cent, the red cell count, 1,600,000, and the white cell count, 18,200. In the interim the patient had been attending school and playing games, and had no complaint. There had been an occasional attack of abdominal pain but no constipation. It should be noted that roentgenograms of the chest indicated for the first time some changes at the base of each lung and calcified glands suggesting tuberculosis. He was jaundiced as before, the heart was slightly enlarged, and there was a systolic murmur at the apex transmitted to the axilla. The liver was greatly enlarged, and the spleen was not palpable. A series of roentgenograms of the gallbladder showed a normal condition.

Since then the patient has been seen on several occasions in the dispensary, and has gained strength, is going to school and is carrying on his usual line of activity.

CASE 2.—*Sickle cell anemia previously recognized. Generalized abdominal cramps, vomiting, slight general abdominal tenderness and distention. Temperature, 100.2 F. White blood cell count, 20,000. Pain increasing. Exploratory laparotomy. Negative findings. Pneumonia postoperatively.*

Helen W., a 10 year old Negro girl, was admitted to the hospital on Nov. 2, 1932, because of severe, generalized abdominal cramps of twelve hours' duration. She had been constipated for three days but had not vomited. Occasionally the pains seemed worse on the left side, but the patient was not sure. She was known to have sickle cell anemia and had a somewhat similar attack three years previously. Several months previously she had pain in one extremity which was thought at first to be due to acute osteomyelitis.

Physical examination revealed: temperature, 99 F.; pulse rate, 110; respiratory rate, 32, and white blood cell count, 20,000. The heart and lungs were normal. There was a subicteric tint to the scleras. The patient was writhing in pain. The abdomen was slightly distended and was held rather tense. There was moderate tenderness over the abdomen, but no real muscle spasm or localized pain was noted. The liver and spleen were not palpable.

It was believed that this was probably a manifestation of the sickle cell anemia or possibly central pneumonia; so the patient was observed for nine hours. During that time the pain increased in frequency and severity and she began to vomit. An enema was not effective. She kept her thighs flexed constantly. The temperature rose to 100.2 F. Since it seemed possible that appendicitis or early ileus was present, an exploratory laparotomy was done by Dr. I. Ridgeway Trimble. No abnormality could be found. The appendix was removed and was normal. Convalescence was stormy, owing principally to pneumonia at the base of each lung. The abdominal pain subsided on the third postoperative day. The leukocyte count remained high for several days, and on the sixth postoperative day rose to 46,000. The hemoglobin content was 76 per cent at first but dropped to 42 per cent on the tenth postoperative day, the red blood cell count at that time being 1,800,000 and the white blood cell count, 58,000 with 79 per cent polymorphonuclear leukocytes. Marked sickling was present. There was slight albuminuria, the tuberculin and Wassermann reactions were negative, and a blood culture was sterile. The pneumonia began to resolve rapidly by the fifteenth postoperative day, and the patient was soon much improved.

Since then she has been followed in the dispensary. On one occasion she had an attack of mild pain in the upper portion of the abdomen and constipation which lasted for four days and was not relieved by enemas. The temperature was normal and the white blood cell count was 20,000. There was diffuse tenderness in the upper portion of the abdomen but no muscle spasm. Since then she has had no abdominal pain.

CASE 3.—*Abdominal pain, nausea and constipation. Known to have sickle cell anemia. Temperature, 98 to 100.2 F. Tenderness and muscle spasm in the hypochondrium on the right and at McBurney's point. No jaundice. White blood cell count, 20,000; hemoglobin, 50 per cent. Appendicitis and cholecystitis simulated. Gradual disappearance of pain.*

Eugene A., a 14 year old Negro, was admitted to the Harriet Lane Home for the fourth time with the complaint of abdominal pain of eighteen or twenty hours' duration. He had been nauseated but had not vomited or had diarrhea.

There had been no bowel movement for two or three days. On the previous evening he complained of slight pain in the left side of his chest. His mother said that he had been having attacks of abdominal pain every few weeks and that he tired easily and had dyspnea on exertion.

The past history was of interest in that the patient had been admitted on three previous occasions, on the first of which sickling was found. From 2 to 4 years of age he had recurring attacks of abdominal pain and fever, though he was not observed during any of these attacks. At that time there were noted general glandular enlargement, absence of jaundice, slight cardiac enlargement, the edge of the liver 3 fingerbreadths below the costal margin and an otherwise normal abdomen. The white blood cell count was 15,000, 24 per cent being polymorphonuclears, 3.5 per cent eosinophils, 7.5 per cent neutrophilic myelocytes and 48 per cent lymphocytes. From the age of 7 to 13 he again had attacks of pain, "abdominal cramps" and headache, and mild jaundice was noted. There had been one attack in which he complained of cramplike pain in the abdomen, elbows and knees with numbness in the fingers and toes. He was observed again in the hospital. This time the liver was not palpable, and there was marked anemia (hemoglobin, 40 per cent; red blood cell count, 1,700,000). Roentgenograms of the skull showed thickening of the outer table, principally in the vertex, with a peculiarly granular appearance.

On examination the temperature, pulse and respiratory rate were found to be normal. The patient was well nourished and did not look very sick but had considerable abdominal pain. There was no jaundice or icteric tinge to the scleras. The heart was a little enlarged, and a systolic murmur was transmitted a short distance beyond the axillary line. The abdomen was not distended but rounded and moved only fairly well on respiration. There were marked tenderness and muscle spasm in an area about 5 or 6 cm. in diameter just beneath the costal margin in the mammary line. No masses could be felt, and one could not be sure whether the liver was enlarged because of the muscle spasm. There was another area of about the same size at McBurney's point where there were definite tenderness and rigidity. There was rebound pain over the region of both the gallbladder and the appendix. Elsewhere, the abdomen could be palpated quite deeply without causing pain. There was a leukocyte count of 20,500, with 60 per cent polymorphonuclears and 30 per cent lymphocytes. The red blood cell count was 1,900,000, the hemoglobin content was 50 per cent, and there was marked sickling in the preparation of fresh blood (30 per cent immediately and 100 per cent in twelve hours). The urine was normal.

Although it was known that the patient had sickle cell anemia, my associates and I were aware that such a patient is just as subject to the acute abdominal diseases as other people. With such tenderness in the region of the appendix and gallbladder, together with nausea, constipation and leukocytosis, some concern was felt. With the history of previous attacks of abdominal pain it was decided to observe him a few hours. An enema was administered which proved effectual and partially relieved the pain in the right lower quadrant. Eight hours later the tenderness and muscle spasm had disappeared, and although tenderness and muscle spasm remained in the right upper quadrant there was no spontaneous pain. Gradually over a period of four or five days the signs and symptoms at the right costal margin disappeared. Very slight icterus appeared which subsided in a few days. A month later the patient again complained of abdominal pain which was generalized but most annoying on the right side. There was slight tenderness over the edge of the liver, which could just be palpated. The white blood cell count was 19,000; the hemoglobin content was 42 per cent, and sickling was

active. Urobilin was present in the urine in a large amount. The urine was not remarkable except for a persistently low specific gravity (from 1.008 to 1.002). The patient has had no complaint during the past six months.

It is interesting to note the similarity in the abdominal findings in this case and in that of Smith (1928). In each there were separate and distinct areas of tenderness and muscle spasm over the gallbladder and the appendix.

CASE 4.—*Sickle cell anemia and priapism. Attacks of epigastric and hypochondric pain on the right radiating to the back. Bile in stool variable in amount. Cholecystectomy for cholecystitis and cholelithiasis. Normal convalescence except for slow healing of cutaneous edges. Death one year later of circulatory failure and bronchopneumonia. Autopsy.*

On Aug. 2, 1925, Willie B., a 23 year old Negro, was admitted to the urological service with priapism. This condition was successfully treated by aspiration of blood clots from the corpus cavernosum. The patient was found to have active sickle cell anemia and was then transferred to the medical service. He was well developed and well nourished. There were jaundice and general glandular enlargement. The heart was a little enlarged, and a systolic murmur was audible at the apex. There were moderate tenderness and muscle spasm in the hypochondrium on the right side. The results of the abdominal examination otherwise were not remarkable; the spleen was not palpable. During the next six weeks his temperature varied from 99.4 to 103 F. The red blood cell count was 2,200,000; the hemoglobin content, 60 per cent, and the color index, 1.36. The white blood cell count varied from 13,700 to 45,000, with a normal distribution of cell types. There was some albuminuria. Roentgenograms of the gallbladder showed numerous stones. On several occasions tenderness over the gallbladder was noted, though the patient complained of very little spontaneous pain during his stay.

He was at home for the following year and continued to have poor health. He had pneumonia with increased jaundice lasting for about a month. Headache, night sweats and loss of weight were the outstanding symptoms for several weeks previous to the next admission. He fainted once. For a period of two weeks he had pains in the knees, shoulders and elbows. There were two attacks of epigastric pain radiating through to the spine, the attacks being followed for a short time by clay-colored stools.

On examination he was found to be deeply jaundiced and very pale, but still moderately well nourished and in no great discomfort. The findings were roughly as before save for more marked tenderness and muscle spasm in the right upper quadrant of the abdomen. The temperature was normal. The blood showed, as before, marked sickling. The red blood cell count was 2,100,000; the hemoglobin content was 54 per cent, and the color index was 1.1. The white blood cell count varied from 12,000 to 18,000. A cholecystectomy was performed on June 25, 1928, by Dr. Deryl Hart, who found a thickened gallbladder filled with many stones. There were no stones in the common duct, which appeared normal in every respect. Convalescence was uneventful save for very slow healing of the cutaneous edges. The patient was discharged considerably improved five weeks after the operation. The van den Bergh reaction was 7.9 mg. per hundred cubic centimeters (direct) as compared with 24.8 mg. (direct) on admission to the hospital.

On April 24, 1929, the patient was admitted to the Baltimore City Hospital to the service of Dr. Thomas R. Boggs, with edema of the feet, ankles and face of five days' duration. Chills, fever and night sweats with anorexia and weakness were complained of. He presented signs of circulatory decompensation, bronchopneumonia and some nephritis. Jaundice and general glandular enlargement were noted as before. The heart was moderately enlarged and the pulse was collapsing.

There was some tympanites with resistance to palpation in the hypochondrium on the right. Albuminuria and cylindruria were marked. The phenolsulphonphthalein test showed only 15 per cent excreted in the first hour. The nonprotein nitrogen content was 125 mg. per hundred cubic centimeters. Death followed in a short time.

Autopsy revealed changes typical of sickle cell anemia in the spleen, hyperplastic bone marrow, cardiac hypertrophy and dilatation, pulmonary edema, bronchopneumonia and congestion of the kidneys with scarring, but little evidence otherwise of nephritis. The liver was normal except for jaundice.

CASE 5.—*Cramplike pains in the lower portion of the abdomen following diarrhea and vomiting simulating acute digestive disturbance. Diarrhea followed by constipation. Subsequent localization of pain in the hypochondrium on the right side. Mild jaundice. Sickle cell anemia demonstrated. White blood cell count, 18,000. Gradual subsidence of pain. Gallbladder not demonstrated by Graham test. Diagnosis: sickle cell anemia with probable cholecystitis.*

On March 21, 1933, Edward B., a 38 year old Negro, was admitted to the hospital because of diarrhea and vomiting of three days' duration and severe cramplike abdominal pain in the previous twenty-four hours. His past history was interesting in that he had noticed weakness in his legs, pain in the joints, constipation and headache. He had lost 25 pounds (11.3 Kg.) in the previous year. There had been no previous attack similar to the present one. He had gonorrhea a few years previously.

The temperature was 102 F., the pulse was 88, the respiratory rate was 26, and the blood pressure was 130 systolic and 80 diastolic. The patient was well developed, did not look ill and was in no great discomfort. The scleras were mildly jaundiced. The general physical examination revealed no abnormality save tenderness and slight rigidity in the hypochondrium on the right side. There was some induration about the prostate. The red blood cell count was 5,800,000; the hemoglobin content was 106 per cent, and the white blood cell count was 18,500 with 81 per cent polymorphonuclears. A preparation of fresh blood showed marked sickling of the erythrocytes. The ven den Bergh reaction was a delayed biphasic response equivalent to 4.7 mg. per hundred cubic centimeters. There was bile but no occult blood or parasites in the stool. The urine contained a few white blood cells, and for the first two weeks urobilin was present. Both eventually disappeared.

On the day of admission the patient vomited several times and became constipated. These symptoms disappeared on the second day, and thereafter he had no complaints during the subsequent month of hospitalization. The tenderness in the right upper quadrant persisted for several days and gradually subsided. The temperature remained at about 101 F. for the first few days and then gradually fell to normal during the following week. The white blood cell count remained at 18,000 for forty-eight hours, then fell to 9,000 on the third and the fourth days, and thereafter was between 4,000 and 5,000, with a normal distribution of cells. There was no increase of fragility of the red blood cells. The red blood cell count and the hemoglobin content remained high. Visualization of the gallbladder was not possible, even after intravenous administration of the dye, and no stones were seen in the roentgenogram.

It was thought that the patient probably had chronic cholecystitis in addition to the sickle cell anemia and low grade prostatitis. He has been well ever since. An operation was not permitted.

CASE 6.—*Generalized cramplike abdominal pain, nausea, mild fever, leukocytosis, boardlike abdominal rigidity and tenderness. Exploratory laparotomy with normal findings. Uneventful convalescence.*

Samuel S., a 36 year old Negro, was admitted to the hospital on Aug. 12, 1934, because of increasingly severe, generalized, cramplike abdominal pain with which he had wakened twelve hours earlier. He said that when the pain became extreme it felt as though it extended into both thighs anteriorly. He had taken a cathartic at once, which was followed two hours later by a bowel movement without relief of symptoms. He had been nauseated but had not vomited. There was no history of previous indigestion, abdominal pain or jaundice.

His past history was interesting in that he had an attack of severe abdominal pain in 1929, after which he was treated with ice-pack for what was termed appendicitis. Three months subsequently he was operated on in another hospital for what he was told was a ruptured appendix, and the abdomen was drained. In 1932 he returned to the same hospital with severe abdominal pains, and the abdomen was explored a second time. He did not know what the findings were but asserted that his convalescence was uneventful and that he had been symptom-free since that time. He had "rheumatic" pains in the knees and joints from the age of 12 to 23. These would be present for a day or even a week and then subside, with varying intervals of freedom followed by a recurrence in some other joint, such as the elbow or shoulder. There was never redness, swelling or tenderness of the joints. During the past two or three years he had occasional mild pain in the joints without fever and without having been incapacitated. He was never sickly as a child or as an adult, nor had members of his family been considered weak or delicate. He worked regularly as a laborer, and except for the aforementioned episodes had been perfectly well. He had gonorrhea five years previous to admission to the hospital.

On examination the temperature was 99.4 F.; the pulse rate, 100; the respiratory rate, 26 to 30, the blood pressure, 165 systolic and 110 diastolic, and the urine, normal. The patient was a strong, robust looking Negro who complained bitterly of severe abdominal pain. He looked sick. His thighs were flexed, and he guarded his abdomen carefully. His color was good, and he had no cough, but the alae nasi dilated with each inspiration. There was no jaundice and no general glandular enlargement. Examination of the heart and lungs gave negative results. The white blood cell count was 13,000, and the hemoglobin content was 90 per cent.

The abdomen was symmetrical and slightly distended and moved very little on respiration. There were an old, well healed low right rectus incision, and a drainage stab wound in the right flank, neither of which was tender or contained a hernia. Generalized tenderness and boardlike rigidity were present over the entire abdomen, perhaps a little more pronounced in the region about the umbilicus, but at no point could one palpate deeply. Hepatic dulness was present. The pain seemed to be constant. It was my impression that he had peritonitis, possibly from a perforated ulcer, and a laparotomy was advised and performed. There was no peritonitis and no free fluid, and the stomach and intestine everywhere appeared normal. A few omental adhesions about the old incision were present. The gallbladder was thin-walled, soft, contained no stones and could be emptied on pressure. The liver was normal in size and consistency. The pancreas was normal. It was then found that the spleen was enlarged to about twice its normal size. It was firm, nodular and adherent to the diaphragm. We then suspected that this was a case of sickle cell anemia, and a smear of fresh blood showed immediate sickling of the red blood cells. The patient's convalescence was uneventful.

Further study revealed that the hemoglobin content was 90 per cent or more and that the red blood cell count was 4,000,000. The sedimentation rate was 15 mm. per hour, and the icterus index was 11. The van den Bergh reaction showed an "indirect trace." The leukocytosis disappeared in a few days. The hemoglobin content remained high, and the urine remained normal except for a low fixed specific gravity by the Mosenthal test. The variation in specific gravity was from 1.009 to 1.014.

This case was particularly interesting, not only because of the boardlike rigidity of the abdomen and the picture of severe peritoneal irritation but also because of the lack of jaundice and the general good health.

ABDOMINAL MANIFESTATIONS

Many patients with the active form of the disease have at some time attacks of acute abdominal pain, fever, mild jaundice and leukocytosis. The pain may be in the left upper quadrant, suggesting splenic infarcts, or in the epigastrium and right upper quadrant, simulating cholecystitis or hepatic tenderness from other causes or even gastric or duodenal disease. Again, there may be a cramplike pain, either generalized or localized in the epigastrium, associated with nausea, vomiting, obstipation and distention and strongly suggesting intestinal obstruction. Instances are known in which acute appendicitis has been mimicked, and on occasions acute salpingitis has been erroneously diagnosed. The symptoms and signs may vary in the same person from day to day, so that more than one abdominal condition is portrayed.

Perhaps the most common type of pain is that which occurred in the first case reported (Herrick [1910]). The patient described these episodes as "bilious attacks" with severe epigastric pain, vomiting, slight jaundice and, later, dark urine. The duration may be from a few hours to several days. The jaundice is not of the obstructive type. Often there is some muscle spasm (Mason [1922]), particularly tenderness over a palpable edge of the liver; the temperature may range up to 102 or 103 F., and the white blood cell count, though usually from 15,000 to 20,000, may be over 60,000. It is possible to have an attack at a time when there is no jaundice (Huck [1923], cases 1 and 2). Epigastric pain and pain in the left upper quadrant (Sydenstricker, Mulherin and Houseal [1923]; Anderson [1926]) sometimes coming on after meals may strongly suggest the presence of a gastric ulcer. On the other hand, pains in the hypochondrium on the right side are not infrequently due to actual cholecystitis and cholelithiasis. Washburn (1911) and Hamilton (1926) have reported such instances, and of the six patients whose cases are reported here, one (case 4) was proved to have gallstones and another (case 5) probably had them.

In another group the condition clearly simulates appendicitis, for example, in cases of J. Levy (1929, first reference), Leivy and Schnabel (1932), Dreyfoos (1926), Smith (1928) and in cases 2 and 3 reported

here. There may be generalized cramplike abdominal pain, nausea, vomiting, constipation, fever and leukocytosis, with generalized tenderness or pain and rebound tenderness in the right lower quadrant. Jaundice is not necessarily present at first, and neither the liver nor the spleen may be palpable. In case 3 icterus was not noticeable at the onset, though mild jaundice developed a few days subsequent to the attack. In case 2 there was some difference of opinion at the onset as to whether or not mild jaundice was present. Each patient was observed for several hours after admission; in case 3 the symptoms lessened and the tenderness over McBurney's point almost entirely disappeared after an enema, while in case 2 the picture became more and more indicative of appendicitis, eventually leading to an exploratory operation with normal findings.

In other instances, for example in cases 1 and 6, the history of cramplike abdominal pains, vomiting and obstipation together with tympanites force one to consider intestinal obstruction. The pains may be in the lower portion of the abdomen and suggest salpingitis, as in the case reported by Ching and Diggs (1933). Again, the pain may appear in different places at various times in the same person and cause more than one diagnosis to be made (Leivy and Schnabel [1932]).

In view of these protean manifestations, it seems possible that a number of cases of unexplained pain in the abdomen or extremities in Negroes may be due to sickle cell anemia.

DIAGNOSIS

There are obviously two steps in the diagnosis: first, the establishment of the presence of sickle cell anemia and, second, the decision that the abdominal symptoms are or are not attributable to this disease. If this form of anemia is suspected its presence may readily be proved by the proper examination of a preparation of fresh blood.[2] The second problem is more difficult. If the signs and symptoms are such that the patient may be observed for some time the condition will usually improve and an operation may be obviated. On the other hand, it is to be borne in mind that a real emergency may exist, and if there is no amelioration one may be forced to explore the abdomen. In the ultimate analysis the surgeon must rely on his experience in judging abstractly whether or not an immediate exploration is indicated. A history of previous similar attacks with jaundice is most helpful in making the decision.

Leukocytosis is usually present in the abdominal crises of sickle cell anemia and is often much higher than that which would be expected of

2. A small drop of blood is placed on a no. 1 cover-slip, and the latter is inverted on a glass slide and sealed with petrolatum.

the disease simulated. No reliance, however, can be placed on this as a diagnostic point, for abdominal crises have been reported in which there was slight leukocytosis or none.

It is well to bear in mind that jaundice due simply to uncomplicated sickle cell anemia is not obstructive, that there are hyperbilirubinemia, hyperurobilinuria and usually an indirect van den Bergh reaction and that urobilin is present in the highly colored stools. The temperature is often elevated to 101 or 102 F., and has been seen at 104 F. on several occasions. There is likely to be low gastric acidity and an absence of occult blood in the stool. Attacks of pain simulating acute osteomyelitis, acute arthritis or rheumatic fever may occur in patients who are subject to these abdominal crises.

The cause of the pain is unknown. The most widely accepted theory is that it is due to infarcts in the spleen or to the perisplenitis which is so frequently noted at autopsy. These could account for many of the symptoms, particularly the pain in the left upper quadrant and epigastrium and perhaps the tympanites. On the other hand, they do not so readily explain the pain and tenderness in the right upper quadrant and over McBurney's point or that in the lower part of the abdomen. Furthermore, in the cases of Leivy and Schnabel (1932) and of Landon and Lyman (1929) identical abdominal crises recurred after the spleen had been removed. Bothe's patient apparently continued to have similar if not such severe attacks after splenectomy. The embolus in the hepatic artery which was suggested in the case of Yater and Mollari (1931) was not proved. Thrombosis in the liver is not common. It is conceivable that the enlargement of the liver may in some way be responsible for the hypochondriac pain on the right side, but this is not likely. Certainly gallstones occur in some persons (Miyamoto and Korb [1927]; Washburn [1911]; Hamilton [1926]; Graham [1924], and case 4, reported here) and are responsible for hypochondriac pain in the right side, but there are patients with similar pain who have no cholelithiasis or cholecystitis (Hamilton [1926]). Constipation is often associated with the attacks, but no changes have been noted in the colon. It has been suggested that changes in the spinal cord or even pain from nerve roots due to bony changes in the vertebrae were responsible (Leivy and Schnabel [1927]), but this has not been established.

TREATMENT

There is no specific therapy for the disease or for the abdominal crises. General supportive measures, hygienic improvements and transfusions if the hemoglobin concentration is very low are customarily employed for the disease itself. For the abdominal manifestations a policy of watchful waiting with mild sedatives, heat and enemas is all

that seems advisable. Torrance and Schnabel (1931; 1932) have recommended the use of potassium sulphocyanate and have advanced an interesting theory as to the rapidity of erythrocytic clumping. Splenectomy is not recommended (Hahn and Gillespie [1927]; Stewart [1927]; Bell et al. [1927]; Hahn [1928]; Landon and Lyman [1929]; Leivy and Schnabel [1932]; Bothe [1933]).

Patients with this disease not seldom become candidates for some form of operative therapy unconnected with the anemia. It has been my experience that patients with the latent form stand such procedures as well as other people but that those patients in whom the disease is or has been in active phase may occasionally do very badly. One such patient underwent a simple hysterectomy and salpingectomy. Before operation her general condition was good and the hemoglobin content was 90 per cent, the white count was 8,500, and she stood the actual operative procedure well. Two days later there developed what was apparently a crisis of the anemia; the hemoglobin content fell rapidly, while the white blood cell count varied from 27,000 to 60,000. She was irrational and had marked tachycardia, and on the fifth postoperative day jaundice became pronounced and increased rapidly until death on the seventh postoperative day. The autopsy showed a rather large spleen characteristic of sickle cell anemia with infarcts, necrosis and adhesions. There was some midzonal necrosis of hepatic cells, with moderate pulmonary and cerebral edema. The case of the patient of Ching and Diggs (1933), who died shortly after a laparotomy, is probably another case in point.

SUMMARY

Attacks of acute abdominal pain occur not infrequently in sickle cell anemia. These attacks may be quite severe and may be accompanied by nonobstructive jaundice, fever, muscle spasm, leukocytosis, nausea and vomiting. The pain is usually in the upper portion of the abdomen, in the epigastrium or in the left or the right upper quadrant. It may be so situated as to simulate cholecystitis, appendicitis or salpingitis, or the picture may suggest ileus. Patients with this condition are subject to the same abdominal diseases as are other persons, so it is important for the surgeon to be familiar with this phase of sickle cell anemia. Attacks of pain in the bones or joints not unlike acute osteomyelitis or acute rheumatic fever are well known. A history of previous abdominal crises with jaundice is one of the more important points in deciding whether or not a patient has pain from sickle cell anemia or from one of the more familiar abdominal diseases.

Patients with latent sickle cell anemia usually stand operative procedures well; those with the active form present a better risk than their general condition or degree of anemia would seem to indicate.

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CHANGES PRODUCED BY VARIOUS OPERATIONS ON THE STOMACH

SHOWN BY THE USE OF A MODIFIED ACID TEST MEAL

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Posterior gastro-enterostomy performed in properly selected cases has long been accepted as one of the most satisfactory procedures in the treatment of duodenal ulcer. Two reasons have generally been advanced in explanation of its efficacy. First, it has been stated that the formation of a gastro-enterostomy stoma allows the gastric contents to pass into the jejunum without going through the duodenum, thereby removing the irritation of acid and food and allowing the ulcer to heal. Roentgenologists have taught, however, that in most patients unless the pylorus is completely obstructed the gastric contents leave the stomach to a large degree not through the gastro-enterostomy stoma but through the pylorus; and in spite of the fact that the ulcer continues to be exposed to the irritation of gastric contents, though perhaps for not so long a time, it usually proceeds to heal. The second explanation which has been offered is that gastro-enterostomy or one of various similar operations brings about a reduction in gastric acidity by allowing the duodenal contents to regurgitate into the stomach and neutralize the acid. The evidence in favor of this theory which has been obtained by the use of a test meal of the Ewald type is not entirely satisfactory. The reduction in acidity as found by most observers is small in amount and not always demonstrable.

Thus, Wilensky and Crohn [1] studied patients from one to four years after posterior gastro-enterostomy, posterior gastro-enterostomy with exclusion of the pylorus, pylorectomy or partial gastrectomy had been performed and found only a slight decrease in acidity. Lewisohn and Feldman [2] found that the acidity was reduced in nine of twelve cases of posterior gastro-enterostomy and in twenty-eight of fifty cases of

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gastro-enterostomy with pyloric exclusion (Berg's method) in which the patient was examined from three to five years after the operation. In eight of the same series the acidity was higher than before operation. Lewisohn [3] concluded after a study of ninety-two cases of gastro-enterostomy with or without pyloric exclusion that after a lapse of many years the acidity was practically unchanged, and he advised a more radical procedure for the treatment of peptic ulcer.

More striking evidence of definite change produced by gastro-enterostomy is obtained when an acid meal consisting of from 100 to 300 cc. of from 0.3 to 0.5 per cent hydrochloric acid is substituted for the Ewald type of meal. The use of an acid meal furnishes an index of another factor, the ability of the stomach to reduce excess acidity. Olch [4] administered an acid meal to a series of dogs before and after gastro-enterostomy, a Finney pyloroplasty or a Polya resection and found that these operations resulted in a more rapid reduction in the strength of the acid, the efficiency of the procedures in producing this reduction being in the order given. Elman and Rowlette [5] performed a modified Rammstedt operation on dogs and found increased neutralization of the acid test meal and also an increase in the emptying time of the stomach. Elman [6] also gave the acid meal to patients before and after gastro-enterostomy and found that the operation increased the amount of reduction of the acid. It is of interest that he noted in studying patients with duodenal ulcer and some patients with a certain amount of pyloric obstruction that before operation there was a diminished ability of the stomach to reduce the acidity of the meal.

Since we [7] have shown that the reduction which occurs in the acidity of an acid test meal introduced into the intact stomach is due mainly to dilution and not to neutralization, it seemed of value to investigate further the nature and importance of this phenomenon after various operative procedures used in the treatment of duodenal ulcer had been performed.

METHODS

The acid meal that we used consisted of 300 cc. of approximately tenth-normal hydrochloric acid in which was dissolved a small amount of the sodium salt of phenolsulphonphthalein. The phenolsulphonphthalein becomes red when alkalinized, and changes in its concentration can be accurately determined by means of a colorimeter, with an alkalinized portion of the original solution

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used as a standard. We have found that if 12 mg. of the sodium salt of phenolsulphonphthalein is added to 1,100 cc. of the acid solution the color resulting when a portion of it is alkalinized will be most satisfactory for colorimetric determinations.

All the experiments were performed on healthy dogs which had been fasting for approximately twenty-four hours. Before the acid meal was introduced the contents of the stomach were aspirated, and the stomach was thoroughly lavaged with a portion of the acid solution of phenolsulphonphthalein. The acid meal was then introduced by a stomach tube, and 1 mg. of histamine was administered intramuscularly. We used histamine in all the experiments in order to reproduce as much as possible the conditions in a secreting stomach. At the end of one-half hour the acid meal was removed from the stomach and another 300 cc. of the acid solution of phenolsulphonphthalein was introduced. This was repeated one-half hour later, and the last meal was withdrawn at the end of the third half-hour period. There were thus used three distinct meals covering a period of one and one-half hours after the injection of histamine. The procedure was carried out at least four times on each dog on different days, and then the animal was subjected to the operative procedure. At the expiration of two weeks or longer four more experiments were done. Our results are thus based on observations on a minimum of four series of experiments, each consisting of three acid meals before operation and the same number after operation.

The chloride content of the acid meal was determined before it was introduced into the stomach. After each meal was removed from the stomach its quantity was measured and a sample was tested for bile by the Pettenkofer method. The percentage of phenolsulphonphthalein was determined by means of a colorimeter, and a portion was then analyzed for total and mineral chloride content. We have given elsewhere[8] details of the methods used to determine the concentration of chlorides, and these will not be repeated here.

CALCULATIONS

Phenolsulphonphthalein Readings.—This indicates the percentage of the original acid meal which is present per hundred cubic centimeters in the fluid removed from the stomach. Reduction in the percentage of phenolsulphonphthalein means that fluid has been added to the acid meal while it was in the stomach. This diluting fluid comes from three sources: (1) acid secreted by the stomach; (2) mucus secreted by the stomach, and (3) fluid regurgitated from the duodenum into the stomach.

Determination of Chloride Content.—Total Chlorides: This content, when determined on the acid meal before its introduction into the stomach, is all acid chloride. After the meal has been in the stomach, however, the total chloride content represents not only the acid chloride of the original meal and the chloride resulting from neutralization of some of the test meal but also the chloride which has been added by secreted mucus and acid and regurgitated duodenal fluid.

Mineral Chloride: This content is determined on the samples removed from the stomach and represents neutral chloride. It is the chloride of neutralized acid, secreted mucus and duodenal content.

Acid Chloride: This is the difference between the concentration of total chloride and that of mineral chloride. It represents unneutralized acid from the test meal and acid secreted by the stomach and not neutralized.

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Total Chloride Corrected for Dilution: The chloride content of the original acid meal multiplied by the reading for phenolsulphonphthalein on the meal after its removal from the stomach represents the chloride content which the meal would have at that dilution if the diluting fluid contained no chloride.

Extra Chloride: Since the diluting fluid, whether derived from the stomach or from the duodenum, does contain chloride, the actual content of total chloride of the meal after its removal from the stomach is always higher than the figure obtained by correcting the original meal for dilution. The difference between the two figures is the extra chloride. This is the chloride of the secreted mucus, the acid and the duodenal contents.

Acid Chloride Plus or Minus Corrected Value: The content of acid chloride of the meal after its removal from the stomach may be greater or less than the chloride content of the original meal corrected for dilution. If it is greater the difference is due to acid secreted by the stomach. If it is less the difference represents neutralization.

Total Fluid Entering the Stomach.—The reading for phenolsulphonphthalein subtracted from 100 gives the number of cubic centimeters of fluid which diluted each 100 cc. of the test meal.

Acid Fluid Entering the Stomach.—We [8] have shown that the concentration of chloride of the fundic secretions averages 578 mg. per hundred cubic centimeters and that this is practically all acid chloride. Consequently, if the extra acid chloride of the sample is divided by 5.78, the quotient will be the number of cubic centimeters of acid fluid which entered the stomach and diluted each 100 cc. of the test meal.

Extra Fluid.—The difference between the amount of total fluid and the amount of acid fluid we have called the extra fluid. This is mainly derived from the duodenum and consists of bile, pancreatic juice and succus entericus. A small portion represents mucus secreted by the pyloric region of the stomach.

The table indicates the results obtained in a series of experiments on one dog before and after gastrojejunostomy. Because of lack of space all the data on the other experiments have not been given in tables, but the results are shown graphically in charts.

Three types of operation were performed: gastroduodenostomy, pyloroplasty and gastrojejunostomy. The gastroduodenostomy was an anastomosis between the upper portion of the duodenum, beginning about 3 cm. below the pyloric sphincter, and the anterior surface of the stomach. The pyloroplasty was of the Heineke-Mikulicz type, and at the conclusion of the operation the pylorus would easily admit two fingers. The gastrojejunostomy was performed by cutting the ligament of Treitz and making an anterior anastomosis beginning near the former point of attachment of the ligament on the jejunum. In a few instances we closed the pylorus at a subsequent operation by severing the stomach from the duodenum at the pyloric sphincter and suturing both stumps.

Chart 1 represents the difference between the total and the mineral chloride content, in other words, the acid chloride. This is the actual acidity of the meals after they are removed from the stomach, and if it is desired to translate the figures on milligrams of chloride per hundred cubic centimeters into terms of tenth-normal hydrochloric acid or total acidity they may be divided by 3.55. It will be noted at once when an acid meal is given to a normal dog and histamine is injected intramuscularly that during the first hour there is little reduction in the strength of the acid. Acid of the meal is neutralized, but it is replaced by acid secreted by the stomach. In dog D the strength of the acid, instead of being decreased, actually increased, and never during the one and one-half hour

Complete Data as Obtained on Dog C Before and After Gastrojejunostomy

Solution	Hours	Total Chloride, Mg.	Mineral Chloride, Mg.	Total Chloride Minus Mineral Chloride, Mg.	Phenol-sulphon-phthalein, per Cent	Chloride Corrected for Dilution, Mg.	Extra Chloride, Mg.	Chloride of Acid ±Corrected Value	Volume, Cc.	Bile	Total Fluid Entering Stomach, Cc. per 100 Cc.	Fluid of Acid	Extra Fluid
					Before Gastrojejunostomy								
0.102 normal hydrochloric acid, 353 Mg. chloride	½	369	30	339	89	314	55	+25	340	0	11	4	7
	1	369	30	339	90	318	51	+21	246	0	10	3	7
	1½	354	44	310	93	328	26	−18	282	0	7	0	7
	½	372	31	341	89	314	58	+27	306	0	11	5	6
	1	390	30	360	83	293	97	+67	318	0	17	12	5
	1½	372	26	346	92	325	47	+21	296	0	8	3	5
	½	367	48	319	85	300	67	+19	233	0	15	3	12
	1	375	39	336	86	304	71	+32	332	0	14	6	8
	1½	366	26	340	90	318	48	+22	246	0	10	4	6
	½	372	30	342	89	314	58	+28	310	0	11	5	6
	1	366	19	347	93	328	38	+19	311	0	7	3	4
	1½	366	24	342	94	332	32	+10	356	0	6	2	4
					After Gastrojejunostomy								
0.101 normal hydrochloric acid, 352 Mg. chloride	½	361	92	269	76	268	93	+ 1	306	++	24	0.2	23.8
	1	366	84	282	79	278	88	+ 4	340	+++	21	0.7	20.3
	1½	354	80	274	83	292	62	−18	280	+	17	0	17
	½	373	73	300	76	268	105	+32	316	++	24	6	18
	1	375	44	331	85	299	76	+32	246	+	15	6	9
	1½	364	84	280	81	285	79	− 5	306	+++	19	0	19
0.101 normal hydrochloric acid, 348 Mg. chloride	½	366	84	282	74	258	108	+24	330	++++	26	4	22
	1	360	95	265	72	250	110	+15	330	++++	28	3	25
	1½	348	91	257	79	275	73	−18	316	+++	21	0	21
	½	372	89	283	73	254	118	+29	368	+++	27	5	22
	1	376	67	309	77	268	108	+41	270	++	23	7	16
	1½	354	80	274	84	292	62	−18	280	++	16	0	16

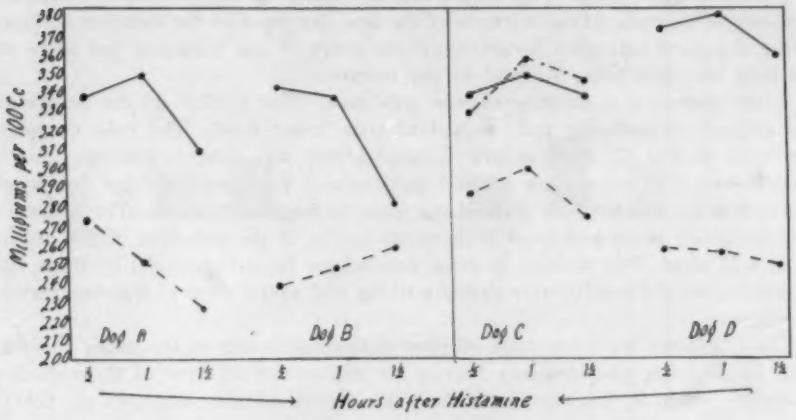

Chart 1.—The acid chloride content of the stomachs of dogs A, B, C and D at half-hour intervals after the administration of an acid meal containing 353 mg. of chloride per hundred cubic centimeters. The unbroken line represents the reading before operation; the broken lines for dogs A and B, the readings after gastroduodenostomy and for dogs C and D after gastrojejunostomy, and the line of dots and dashes, the readings after pyloroplasty.

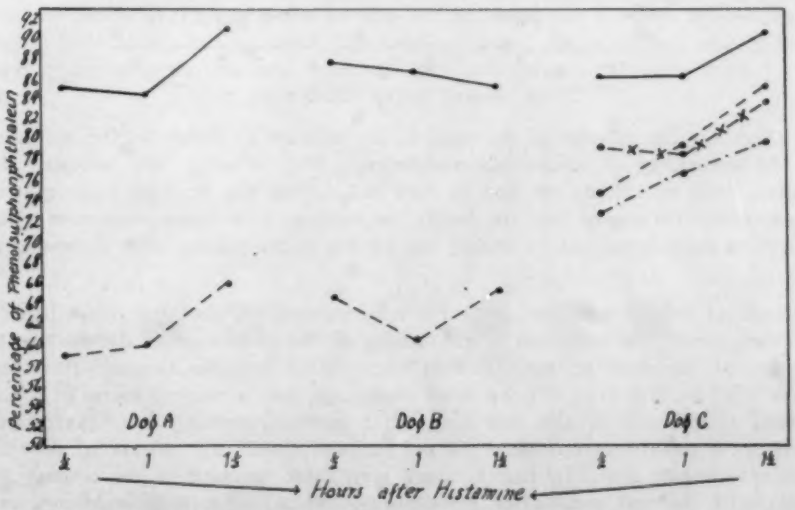

Chart 2.—The dilution of the meal in the stomach as shown by the reduction in the percentage of phenolsulphonphthalein. The unbroken line indicates the reading before operation; the broken line for dogs A and B, the readings after gastroduodenostomy; the line broken with crosses, the readings after pyloroplasty; the line of dots and dashes, the readings after gastrojejunostomy, and the broken line for dogs C and D, the reading after gastrojejunostomy plus closure of the pylorus.

period did it drop to the level of the original meal. In dogs A and B there was considerable decrease in the strength of the acid, but most of the decrease occurred during the third half-hour period, when the effect of the histamine had worn off and little acid was being secreted by the stomach.

After operation a striking change was seen. The acidity of the acid meal was reduced immediately and reached a much lower level. The only exception was seen in dog C, after a pyloroplasty which was done before the gastrojejunostomy. Another dog on which a pyloroplasty was performed but for which figures are not charted here showed the same findings as this one. The operation of pyloroplasty seemed to cause little or no change in the reduction of the acidity of an acid meal. We hesitate to draw conclusions from the results of these two operations, but the results were rather striking and would seem to warrant further investigation.

Chart 2 shows the percentage of phenolsulphonphthalein in the meals removed from the stomach, and obviously here is the explanation of most of the reduction in acidity noted in the previous chart. The curve of the reduction of acidity

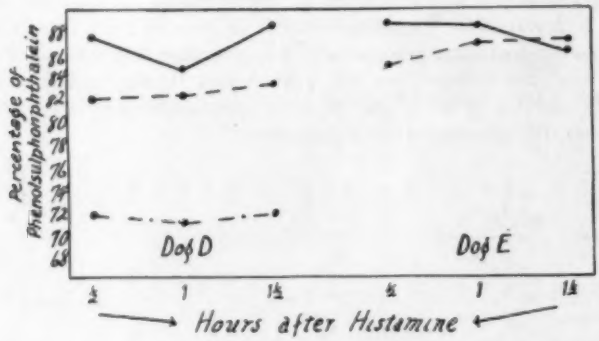

Chart 3.—The dilution of the meal in the stomach as shown by the reduction in the percentage of phenolsulphonphthalein. The unbroken line indicates the reading after operation; the line of dots and dashes, the readings after gastrojejunostomy; the broken line, for dog D, the readings after gastrojejunostomy plus closure of the pylorus, and the broken line for dog E, the reading after pyloroplasty.

corresponds closely with the curve for concentration of phenolsulphonphthalein; in other words, the reduction in the acidity of the acid meal is due mainly to dilution of the meal by nonacid fluid regurgitated into the stomach from the duodenum. In dog D it will be noted that there was a marked increase in the amount of dilution of the test meal after gastrojejunostomy was performed. When at a subsequent operation the pylorus was closed, the amount of dilution was considerably less. In dog C there was some increase in the amount of dilution of the test meal after pyloroplasty, but when gastrojejunostomy was performed later the dilution was increased. Closure of the pylorus again diminished the amount of dilution. Dogs A and B showed the marked increase in dilution which is produced by gastroduodenostomy. Dog E demonstrated the absence of notable change following pyloroplasty and showed why the strength of the acid remained unaltered, as shown in chart 1.

In charts 4, 5 and 6 we have represented graphically the nature and amount of the diluting fluid which enters the stomach. The total amount of fluid entering the stomach per hundred cubic centimeters of the test meal has been charted

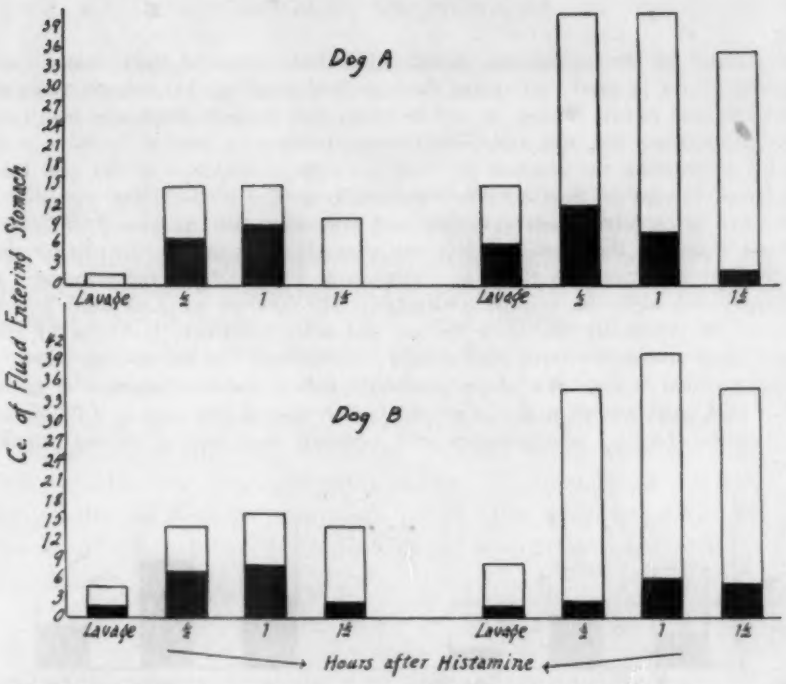

Chart 4.—The nature and the amount of fluid which diluted the test meal in dogs A and B before and after gastroduodenostomy. In this and the following charts the group of four columns on the left indicates the readings before the operation; the group to the right, the readings after the operation; the solid portion of the columns, the acid fluid, and the open portion, the extra fluid.

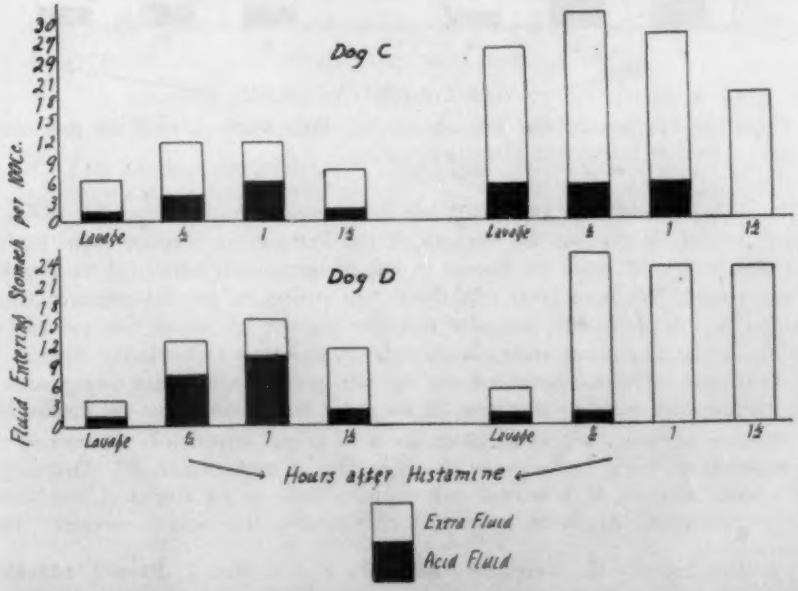

Chart 5.—The nature and the amount of fluid which diluted the test meal in dogs C and D before and after gastrojejunostomy.

and divided, by the calculations already described, into acid fluid, that is, acid secreted by the stomach, and extra fluid or fluid entering the stomach from the duodenum and gastric mucus. It will be noted that there is practically no change after pyloroplasty but that gastro-enterostomy produces a marked increase in the total fluid entering the stomach per hundred cubic centimeters of the acid meal. The total volume of fluid actually removed from the stomach, but not charted here, was essentially the same before and after operation, varying from 240 to 325 cc. More of the meal had left the stomach after gastro-enterostomy than before, but its place was taken by extra fluid, which diluted the remainder of the meal and kept the volume unchanged. The amount of acid fluid will be seen to be practically the same before and after operation, and this in spite of the great amount of extra fluid present; so obviously the neutralizing power of this extra fluid is low. We[7] have previously shown that the reduction in acidity of an acid meal placed in the intact stomach is due 65 per cent to dilution and only 35 per cent to neutralization, and evidently here also a similar relation exists.

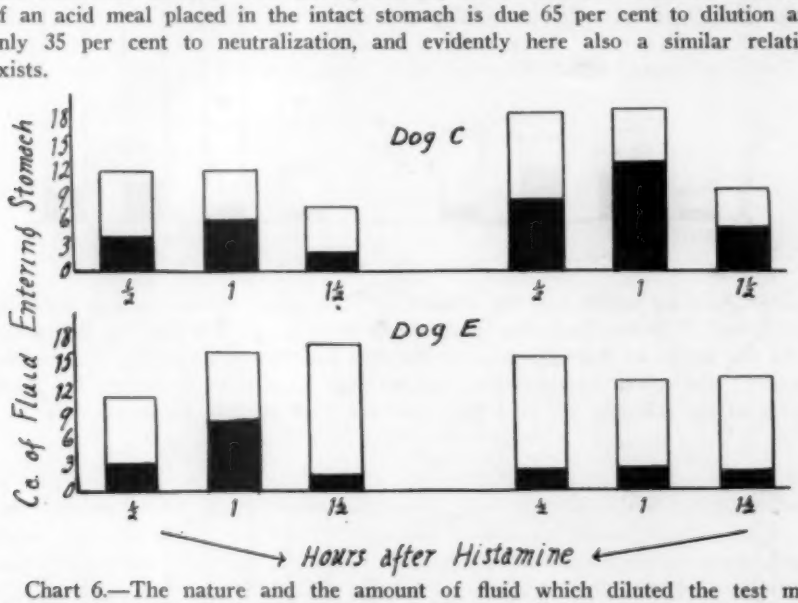

Chart 6.—The nature and the amount of fluid which diluted the test meal in dogs C and E before and after pyloroplasty.

In all experiments the amount of bile in the meals removed from the stomach was estimated by grading the strength of the Pettenkofer reaction from 1 plus to 4 plus, and in all cases the amount of bile present closely paralleled the amount of extra fluid. We have previously shown[9] in studies on pouches prepared from the pyloric region of the stomach that the amount of mucus the pylorus is capable of secreting is not great enough to be an important factor in the dilution of the test meal. The increased amount of bile present after gastro-enterostomy was confirmatory evidence that most of the extra fluid comes from the duodenum.

Another incidental finding to which we wish to call attention is the content of the stomach as found by lavage at the beginning of each experiment. Ordinarily the resting stomach of a normal dog contains little or no free acid, but after gastro-enterostomy has been performed considerable free acid is present. The

9. Wilhelmj, C. M., Neigus, I., and Hill, F. C.: Am. J. Physiol. **107**:490, 1934.

significance of this finding we are unable to explain, but it may have some etiologic relationship to the occasional occurrence of jejunal ulcer following gastro-enterostomy in dogs.

CONCLUSIONS

1. When an acid meal is introduced into the stomach of a normal dog and histamine is given intramuscularly, the strength of the acid shows little change or is increased during the first hour and then is gradually reduced. Reduction in the strength of the acid meal during the first hour is compensated for by acid secreted by the stomach. At the end of an hour the stimulus from the injection of histamine has worn off and the acid is usually reduced in strength. After gastro-jejunostomy the reduction in acidity is strikingly increased. After gastroduodenostomy the reduction is even more marked. After a Heineke-Mikulicz type of pyloroplasty the amount of reduction is almost the same as in a normal dog. After gastrojejunostomy plus closure of the pylorus the reduction is less marked than after gastro-jejunostomy alone.

2. The amount of dilution of the acid meal by duodenal fluid regurgitating into the stomach closely parallels the reduction in acidity and is the main cause of the reduction.

3. The total amount of fluid present in the stomach one-half hour after the introduction of an acid meal is the same after gastro-enterostomy as before, but this total fluid after operation contains a larger proportion of nonacid or "extra" fluid.

4. The amount of acid secreted by the stomach under stimulation with histamine and not neutralized is the same, per hundred cubic centimeters of the acid meal, after operation as before.

5. The amount of bile in the acid meals after removal from the stomach is directly proportional to the amount of extra fluid.

6. The resting stomach of a dog after gastro-enterostomy contains considerable free acid.

FATAL CASES OF SEPTICEMIA CAUSED BY BACILLUS COLI FOLLOWING GASTRIC OPERATIONS

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A short time ago my interest was drawn to the possible fatal complication of septicemia caused by Bacillus coli following gastric operations. A woman 58 years old, in excellent condition before operation, died eighteen hours after a gastro-enterostomy with a temperature of 41.5 C. (106.6 F.) and signs of vascular collapse. Bacillus coli-communior was recovered in an antemortem blood culture. The postmortem examination revealed no evidence of localized infection, peritonitis or hemorrhage. Death was attributed to overwhelming B. coli septicemia.

The records of gastric operations at the University Hospitals for the last thirteen and one-half years,[1] exclusive of the cases of perforated ulcer, include another fatal case of bacteremia caused by B. coli proved by antemortem blood culture and a third case which was similar to these two in its clinical features but in which no blood culture was taken. Because no record of such cases has been found in a search of the literature it is felt worth while to report this possible complication following an operation on the stomach and jejunum.

Case 1.—A 58 year old white housewife was admitted to the hospital for the third time on May 25, 1934. The history of the illness dated back twenty-one years and was that of gastric ulcer. A sleeve resection of the stomach had been performed in 1925 with resultant relief of symptoms for five years. In 1931 the symptoms reappeared, and they became very severe two months before the last admission to the hospital. The remainder of the history was irrelevant.

The physical examination revealed nothing suggestive of ulcer. On the basis of the history and fluoroscopic examinations a diagnosis of gastric ulcer with retention was made. On May 28 a posterior gastro-enterostomy was performed. Before the operation the temperature was 37.2 C. (98.6 F.), the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 135 systolic and 80 diastolic. The white blood cell count was 8,400. The free hydrochloric acid was 10 degrees and the combined acid, 90 degrees.

The operation was performed with the patient under gas-oxygen-ether anesthesia and lasted two hours and forty-five minutes. The patient's condition at the end of the operation was good; the blood pressure was 110 systolic and 60 diastolic, the pulse rate, 140, and the respiratory rate, 32. Three hours later the patient was cyanotic and the blood pressure started to fall. Five and a half hours after operation the blood pressure was 60 systolic and 48 diastolic. After the

From the Department of Surgery of the University Hospitals.

1. This includes the records of the Lakeside Hospital and the Hanna House.

subcutaneous administration of ephedrine and an intravenous injection of 10 per cent solution of dextrose the blood pressure rose to 90 systolic and 40 diastolic. Three and a half hours after operation the temperature was 37.6 C. (99.9 F.). Seven and a half hours after operation the temperature was 40 C. (104 F.), the pulse rate, 146, and the respiratory rate, 46. The patient's condition was critical. Examination of the lungs revealed only a few moist râles at the base of the left

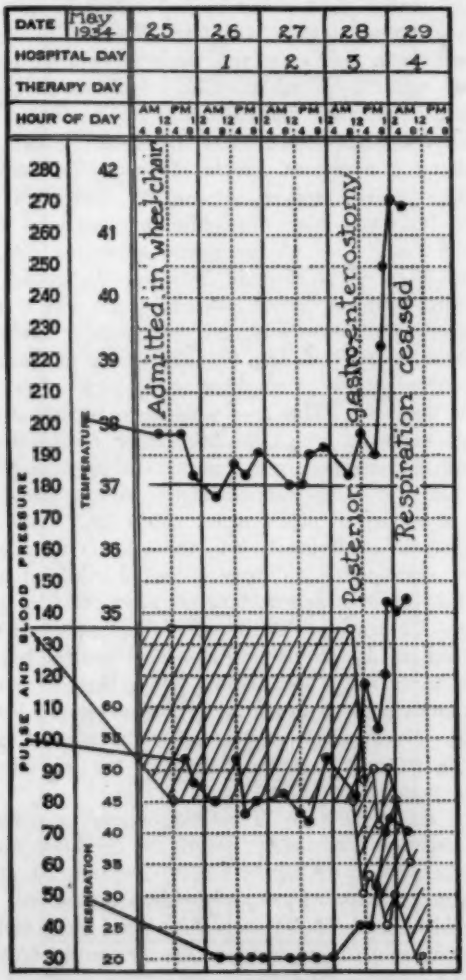

Chart 1 (case 1).—The record of temperature, pulse and respiratory rates and blood pressure immediately before and following the operation.

lung with no evidence of consolidation. The trachea was in the midline and the heart was normal, although the sounds were distant. The patient was not pale. Pneumonia, hemorrhage or septicemia was suspected. A stomach tube was passed and only a few cubic centimeters of blood-tinged fluid was obtained. The abdomen was soft and the stomach was not dilated. In spite of tranfusion

of 500 cc. of whole blood and frequent administrations of caffeine sodiobenzoate the patient rapidly grew weaker. Eleven and a half hours after operation the temperature reached 41.6 C. (106.8 F.), the pulse rate was 140, the respiratory rate was 40, and the blood pressure was 80 systolic and 50 diastolic. The blood pressure continued to fall. Fourteen and a half hours after operation the temperature was 41.5 C., the pulse rate, 144, the respiratory rate, 30, and the blood pressure, 60 systolic and 32 diastolic. The pulse became weaker and the rate more rapid, and the patient died seventeen and a half hours after the operation. A blood culture made ante mortem was later reported to contain B. coli-communis. Though septicemia was suspected, the postoperative course was so short that only one blood culture was taken. Chart 1 shows the rapidly fatal course with the sharp rise in temperature and the fall in blood pressure.

Necropsy disclosed a small gastric ulcer, the recent gastro-enterostomy which was structurally sound, a moderate amount of bronchopneumonia and pulmonary edema, acute fibrinous pleuritis and an old surgical cicatrix of the stomach where the sleeve resection had been done. In addition, there were fatty infiltration of the liver and kidneys and some old peritoneal adhesions. A blood culture five and one-half hours after death showed Bacillus alkaligenes. B. coli was not recovered after death. Midway in the stomach there was a band of scar tissue which extended over both the anterior and the posterior surface from the lesser to the greater curvature, representing the site of the previous sleeve resection. On the posterior surface of the stomach at the pylorus there was a small ulcer measuring 6 mm. in diameter. This area was approximately 2 cm. from the band of scar tissue which extended across the midportion of the stomach. There was no evidence of localized infection, acute peritonitis or hemorrhage.

Case 2.—A 56 year old white married laborer was admitted to the hospital on June 3, 1930, with a history of peptic ulcer. Since 1922 there had been periodic attacks of epigastric pain occurring two to three hours after eating and relieved by food. Roentgen examination on three occasions revealed a deformity of the duodenal cap. In 1924 the free hydrochloric acid after fasting was 74 degrees and the total acidity was 112 degrees. During the six months preceding admission to the hospital the patient had lost 20 pounds (9.1 Kg.) and for two months had vomited nearly everything he ate. The history was otherwise irrelevant.

The physical examination revealed a fairly well developed but poorly nourished man not acutely ill. Examination of the abdomen revealed tenderness on deep palpation in the epigastrium and on each side of the midline. The rest of the examination yielded negative results.

On the basis of the history and roentgen findings a diagnosis of duodenal ulcer with gastric retention was made. Before the operation the temperature was 36.8 C. (98.2 F.), the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 130 systolic and 80 diastolic; gastric analysis showed free hydrochloric acid, 25 degrees, and combined acid, 16 degrees. The white blood cell count was 6,100; the hemoglobin content was 101 per cent, and the differential blood smear contained 77 per cent of polymorphonuclear leukocytes. The vomitus showed a coffee-ground appearance; the benzidine test for occult blood was positive.

At operation, with the patient under gas-oxygen-ether anesthesia, a duodenal ulcer and pyloric obstruction were found. The pylorus was resected, the end of the stomach and duodenum were closed and a posterior gastro-enterostomy (Billroth II) was performed. The operation lasted two hours and fifty minutes. The patient's condition immediately after operation was satisfactory. The blood pressure at the beginning of the operation was 110 systolic and 80 diastolic, rose to a maximum of 150 systolic and 110 diastolic and at death was 95 systolic and 70

diastolic. The pulse rate was 135 at the beginning of the operation, with a maximum rate of 175, and 145 at death. The respiratory rate averaged 30. Three hours postoperatively the blood pressure was 78 systolic and 60 diastolic, the pulse rate, 120, and of fair quality, and the respiratory rate, 28. The patient had short attacks of hiccup, and his hands appeared cyanotic. Examination of the chest

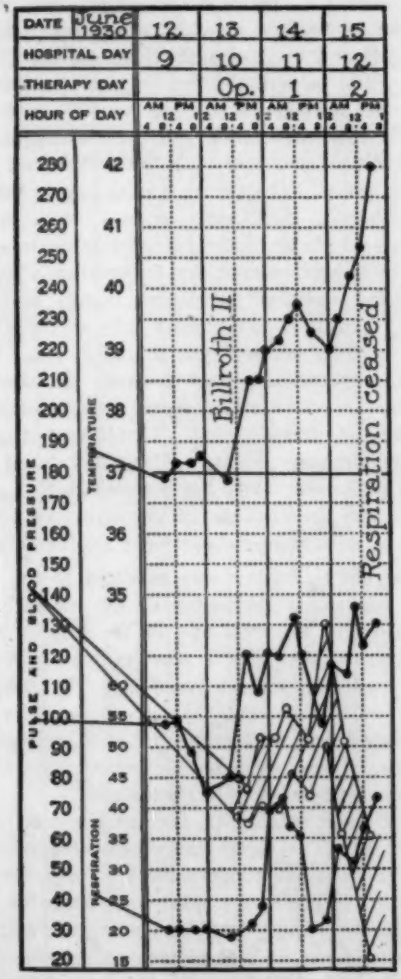

Chart 2 (case 2).—The record of temperature, pulse and respiratory rates and blood pressure immediately before and following the operation.

gave negative results. An infusion of physiologic solution of sodium chloride was given immediately after the operation. Because the blood pressure continued to be low, 300 cc. of a 10 per cent solution of dextrose was given intravenously eight hours after the operation. At this time the temperature was 38.5 C. (99.3 F.) and the blood pressure was 105 systolic and 85 diastolic. Twelve hours after the operation the temperature was 39 C. (102.2 F.), and the pulse rate,

120; the respiratory rate was 40 and there was a Cheyne-Stokes rhythm. The patient was placed on the "danger list." The following day the temperature remained elevated around 39.5 C. (103.1 F.); the blood pressure was 110 systolic and 80 diastolic, the pulse rate was 116, and the respiratory rate was from 22 to 36. The patient continued to have short attacks of hiccup. He was drowsy and slightly cyanotic.

Forty-eight hours after the operation the temperature was 41 C. (104.8 F.), the pulse rate, 124, the respiratory rate, 36, and the systolic blood pressure, 96. Examination of the heart and lungs again yielded negative results. The abdomen was everywhere soft. The patient did not appear anemic. The red blood cell count was 4,200,000; the hemoglobin content was 70, and the white blood cell count was 4,000. This low white blood cell count suggested the possibility of an overwhelming infection. Since there was no evidence of hemorrhage, a transfusion of blood was not given. The course was so rapid that it seemed to exclude the possibility of peritonitis. Septicemia seemed most likely. Accordingly, a blood culture was taken which was later reported to contain B. coli, the type not determined. In spite of the intravenous and subcutaneous administration of fluids, caffeine sodiobenzoate and digifolin, the patient rapidly became worse. The temperature rose to 42 C. (107.6 F.), the pulse rate was 130, the respiratory rate was 42 and the blood pressure was 60 systolic and 20 diastolic. The patient died fifty-two hours after the operation. Chart 2 shows the course of this patient.

Postmortem examination disclosed a recent gastro-enterostomy in which no structural defect could be demonstrated. There was a moderate amount of bronchopneumonia and pulmonary edema. About 250 cc. of old blood and blood clot were found in the peritoneal cavity but not enough to account for the collapse of the patient. There was no evidence of peritonitis or localized infection. A blood culture four hours post mortem revealed B. coli-communior.

Case 3.—A 57 year old toolmaker was admitted to the hospital on Aug. 29, 1929, with symptoms suggesting carcinoma of the stomach. He complained of weakness, of tiring easily, of anorexia and of the loss of 12 pounds (5.4 Kg.) during the preceding two months. For a year he had noticed shortness of breath on exertion and tarry stools on several occasions. The remainder of the history was irrelevant.

He was well developed and well nourished with marked pallor of the skin and mucous membranes. There were no abdominal masses or tenderness. The rest of the examination revealed nothing remarkable.

The white blood cell count was 7,000; the red blood cell count, 3,000,000, and the hemoglobin content, 50. The blood smear presented achromia typical of secondary anemia, and a differential count showed 75 per cent polymorphonuclear leukocytes. The stool gave a strongly positive reaction to benzidine for occult blood. On the basis of the history and the roentgen finding of a large filling defect, a diagnosis of carcinoma of the stomach was made. Before the operation the temperature was 37.5 C. (97.3 F.), the pulse rate, 90, the respiratory rate, 20, and the blood pressure, 110 systolic and 68 diastolic.

On the eighth day of hospitalization, after a transfusion of 600 cc. of whole blood, a moderate-sized carcinoma of the pylorus was resected. The divided end of the duodenum was closed, and a loop of jejunum was anastomosed to the severed end of the stomach. The operation lasted about two and a half hours. During the latter part of the operation the blood pressure fell to 70 systolic and 35 diastolic but responded when dextrose was given intravenously. After the patient was returned to his room the blood pressure continued to be low. Seven hours after the operation the temperature was 38.6 C. (101.6 F.), the pulse rate,

132, the respiratory rate, 37, and the blood pressure, 80 systolic and 50 diastolic. Eleven and a half hours after the operation the temperature reached 40.3 C. (104.5 F.), the pulse rate was 144, and the respiratory rate, 32. A second transfusion of blood given fourteen hours postoperatively failed to improve the condition of the patient. The temperature remained around 40.5 C. (104.9 F.). The pulse became weaker and more rapid. Twenty-four hours after the operation the

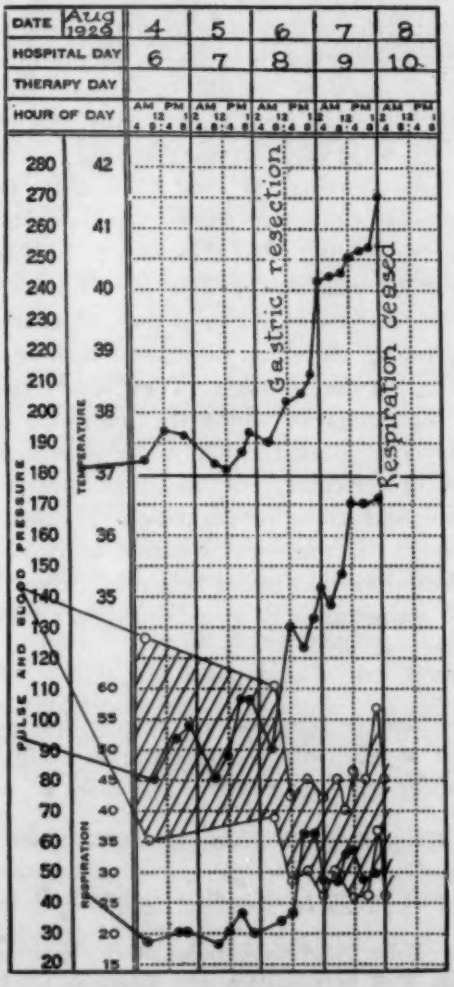

Chart 3 (case 3).—The record of temperature, pulse and respiratory rates and blood pressure immediately before and following the operation.

temperature was 40.5 C., the pulse rate, 172, the respiratory rate, 36, and the blood pressure, 84 systolic and 42 diastolic. Examination of the lungs and heart gave negative results. There was no evidence of peritonitis. Thirty-six hours after the operation the temperature rose to 41.5 C., the pulse became imperceptible, the respiratory rate was 36 and the blood pressure was 80 systolic and 45 diastolic.

The patient died forty hours after the operation. Postmortem examination was not permitted. Unfortunately, no blood culture was taken ante mortem. Chart 3 gives a graphic view of the clinical course of this patient, which is similar to that of the first two patients.

CASES REPORTED IN THE LITERATURE

It seems worth reporting these cases as in the early stage they simulate cases of hemorrhage, they seem to carry a fatal prognosis and no previous report has been found in a search of the literature. Wiens [2] in 1909 reported six cases of B. coli bacteremia, among which was one of a man 45 years old who had a gastrostomy for carcinoma of the esophagus. He died eight weeks after the operation. The antemortem blood culture contained B. coli. The cases described in this report, however, present a different clinical picture from that of Wiens' case except for the bacteremia. The literature to 1924 on B. coli bacteremia has been well summarized by Felty and Keefer [3] who reported twenty-eight cases of their own. In two of these cases the infection came from the intestinal tract. However, in none of their cases did injection follow an operation on the stomach. They stated that the reported cases of B. coli septicemia in which the intestine was regarded as the portal of entry complicated either acute inflammatory processes, like typhoid fever or dysentery, or were subsequent to appendiceal abscesses with thrombophlebitis or peritonitis. Neither in their report nor in those of others [4] is there any mention of cases like those just reported. The false impression might be gained from this that B. coli bacteremia is a rare complication of gastric surgical procedures.

COMMENT

In order to determine the frequency of complication the records of the University Hospital of cases of gastric operation exclusive of cases of perforated peptic ulcer were reviewed.[1] The cases of perforated ulcer

2. Wiens: Zur Kasuistik der Kolibackteriämie, München. med. Wchnschr. **56**:692, 1909.

3. Felty, A. R., and Keefer, C. S.: B. Coli Sepsis, J. A. M. A. **82**:1430 (May 3) 1924.

4. (*a*) Jacob, L.: Ueber Allgemeininfektion durch Bacterium Coli commune, Deutsches Arch. f. klin. Med. **97**:303, 1909. (*b*) Maher, S. J.: Purpura Haemorrhagica: Is It Caused by the Colon Bacillus? M. Rec. **75**:482, 1909. (*c*) Draper, G., quoted by Felty and Keefer.[3] (*d*) Tidy, H. L., and Panton, P. N.: A Note on the Occurrence of the Colon Bacillus in the Blood, Lancet **2**:1500, 1912. (*e*) Holzman, A.: Two Cases of Colon Bacteraemia, Long Island M. J. **7**:376, 1913. (*f*) Widal, F.; Lemierre, A., and Brodin, P.: Four Cases of B. Coli Septicemia, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:963, 1920. (*g*) Pope, B. A.: Quoted by Felty and Keefer.[3] Wiens.[2]

were excluded because it is known that B. coli may enter the b'ood stream in peritonitis. Therefore, it did not seem wise to include those cases in which peritonitis was present before operation. During the last thirteen and one-half years (from Jan. 1, 1921, to July 1, 1934), exclusive of the cases of perforated ulcer, there have been recorded four hundred and sixteen cases from both the private and the ward services at the Lakeside Hospital in which gastric operations have been performed. Of this number seventy-nine patients died in the hospital following the operation. Among these seventy-nine were the two cases reported here in which an antemortem blood culture was reported to contain B. coli. The third case described here closely resembled the first two cases clinically, but no antemortem blood culture or postmortem examination was obtained. In making the diagnosis of B. coli bacteremia it is recognized that the organism should be obtained from the blood during life.[5] It is significant to point out that the two cases of B. coli bacteremia in which the diagnosis was made by antemortem blood culture were of the same frequency as hemorrhage in this series of seventy-nine cases in which death followed operation. They constituted 2.6 per cent if all the cases of gastric operation were included: 3.3 per cent after gastro-enterostomy or partial gastrectomy or 4.5 per cent if the third case is included. My cases followed gastro-enterostomy or partial gastrectomy. Holzman [4e] in 1913 aptly said that B. coli septicemia must always be borne in mind after an operation, especially after laparotomy. The table shows the causes of death following gastric operations and the frequency of B. coli septicemia. In cases 1 and 2 it is difficult to estimate the part played by the bronchopneumonia in the fatal outcome. All that can be said is that anatomically the bronchopneumonia was slight and that death occurred in a much shorter time than is usual in cases of bronchopneumonia. There was no evidence of collapse of the lungs in either case clinically or on the postmortem examination.

It is interesting to speculate on the train of events in these cases. That the operation started the lethal course is evident. It seems likely that the organisms were in the stomach at the time of operation and were thus introduced into the blood stream. It is well known that the stomach may contain B. coli. Cushing and Livingood [6] pointed

5. Miller, J. L.: Bacillus Coli Infections, in Christian, H. A., and MacKenzie, J.: Oxford Medicine, New York, Oxford University Press, 1927, vol. 4, p. 763.

6. Cushing, H., and Livingood, L. E.: Experimental and Surgical Notes upon the Bacteriology of the Upper Portion of the Alimentary Canal, with Observations on the Establishment There of an Amicrobic State as a Preliminary to Operative Procedures on the Stomach and Small Intestines, Johns Hopkins Hosp. Rep. **9**:543, 1901.

this out in 1901. Kopeloff [7] made bacteriologic studies on the gastric juice of 14 psychotic and normal patients by the Rehfuss method and found B. coli present in the patient with the highest gastric acidity. Gillespie [8] in 1892 reported the finding of B. coli-communis in the gastric contents of a patient suffering from gastric dilatation. Both Timozzi [9] and Lucksch [10] reported the finding of B. coli in the stomach of patients with pernicious anemia. These reports indicate that B. coli may be grown from gastric juice with a normal, low or high content of hydrochloric acid. Poppens [11] studied the bacteria of the fasting stomach and duodenum in dogs and found B. coli present in the gastric contents of four of fifteen animals and in the duodenum of twelve of fifteen animals after a period of fasting of from fourteen to twenty-two hours.

Causes of Death Following Gastric Operations Exclusive of Operation for Perforated Ulcer

	Cases		Cases Proved at Autopsy	
	Number	Percentage	Number	Percentage
Bronchopneumonia	27	34.0	15	55
Inanition	11	14.0	5	45
Peritonitis	10	12.8	7	70
Intestinal obstruction	6	7.0	3	50
Unknown	6	7.0	0	0
Pulmonary embolus	3	3.9	0	0
Heart failure	3	3.9	1	33
Hemorrhage	2	2.6	2	100
Septicemia caused by B. coli	2	2.6	2	100
Abscess of the lung	2	2.6	2	100
Suspected septicemia caused by B. coli	1	1.3	0	0
Mediastinitis	1	1.3	0	0
Uremia	1	1.3	0	0
Cerebral embolus	1	1.3	0	0
Thyroid crisis	1	1.3	0	0
Acute pancreatitis	1	1.3	1	100
Disrupted wound	1	1.3	0	0
Total	79		38	48

On the contrary, Palier,[12] in studying the bacteria in the gastric contents of thirteen human patients, failed to find B. coli. Three of these patients had carcinoma of the stomach, one pernicious anemia, four, hypochlorhydria, and five, hyperchlorhydria. Löhr [13] in 1926 studied the

7. Kopeloff, N.: Bacteriologic Studies of Gastric Fractions Obtained by the Rehfuss Method, J. Infect. Dis. **30**:613, 1922.

8. Gillespie, A. L.: The Bacteria of the Stomach, J. Path. & Bact. **1**:279, 1892.

9. Timozzi, F. P.: Colon Bacilli in the Digestive Tract, Klin. Wchnschr. **4**:1017, 1925.

10. Lucksch, F.: The Colon Bacillus in Pernicious Anemia, Med. Klin. **21**: 1200, 1925.

11. Poppens, P. H.: The Bacteriology of the Fasting Stomach and Duodenum, Am. J. M. Sc. **161**:203, 1921.

12. Palier, E.: The Bacteria of the Stomach, M. Rec. **66**:801, 1904.

13. Löhr, W.: Bacteriology of the Stomach, Zentralbl. f. Chir. **53**:1618, 1926.

bacteria in twenty-two cases of perforated gastric or duodenal ulcer and concluded that in surgery of the stomach the colon bacillus was not greatly to be feared. Recent experiments by Johnson and Arnold,[14] who established gastric fistulas in dogs, indicate that the gastric acidity probably has a bacteriostatic power rather than a bactericidal action. These investigators injected B. coli into the previously established fistulas and found that when free acid was detected no viable bacteria could be demonstrated. However, if sterile solution of alkaline phosphate was introduced to neutralize the free acid the original test bacteria reappeared in the culture.

These cases are presented to draw attention to the possibility of B. coli septicemia following a gastric operation even though there is no postmortem evidence of localized infection, such as peritonitis, and that this condition may be rapidly fatal and simulate hemorrhage in the vascular collapse.

SUMMARY

This report is made in order to draw attention to the possible complication of septicemia following operations on the stomach and jejunum.

Two fatal cases, associated with B. coli in the blood stream as shown by antemortem blood culture, are reported. Death of one patient followed gastro-enterostomy for gastric ulcer and that of the other after partial gastric resection (Billroth II) for duodenal ulcer. A third case with similar clinical but without bacteriologic evidence is also discussed.

In the first and third cases no blood studies were made after operation. In the second case the white blood cell count showed leukopenia of 4,000. This aided in the differential diagnosis between overwhelming infection and hemorrhage.

The causes of death in 79 of a series of 416 patients on whom gastric operations were performed are listed. These operations did not include cases of perforated gastric ulcer.

In this series the same number of deaths was attributed to B. coli septicemia as to hemorrhage.

Cases of B. coli septicemia following operations on the stomach and jejunum may have a fatal prognosis and simulate hemorrhage in the sudden vascular collapse and rapidly fatal outcome.

14. Johnson, T. M., and Arnold, L.: Has the Free Gastric Acidity Bactericidal or Bacteriostatic Power? Proc. Soc. Exper. Biol. & Med. **29**:501, 1932.

EXPERIMENTAL STAPHYLOCOCCIC SUPPURATIVE ARTHRITIS AND ITS TREATMENT WITH BACTERIOPHAGE

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Since d'Herelle's [1] discovery in 1917 of the phenomenon to which he applied the term bacteriophagy an extensive literature on the subject has accumulated, an increasing part of which has been devoted to the therapeutic use of this biologic principle in clinical medicine. Perhaps because of the dramatic nature of the phenomenon in the test tube, perhaps because the imagination is so fired by a principle which was to rid the world of bacterial diseases, there has often been a great deal of overenthusiasm in the claims advanced for the therapeutic effects of bacteriophage. Such overenthusiasm, born for the most part of insufficient observation or loosely controlled experiments, has given rise among many serious clinicians to a skepticism which denies to bacteriophage any place in the realm of therapeutics. The misfortune of this situation is that a valuable biologic principle is denied a trial by the very men whose work with it would be most reliable and most helpful. Clearly there is great need of accurate clinical observation on the use of bacteriophage and of carefully controlled experimentation with human beings and animals.

The series of investigations here reported was planned to determine the action of bacteriophage in vivo under conditions which are believed to be as near as possible to ideal for bacteriophagy in the animal body. Before the complicated problem of the action or failure of action of

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1. d'Herelle, F.: Immunity in Natural Infectious Diseases, Baltimore, Williams and Wilkins Company, 1924; The Bacteriophage and Its Behavior, Baltimore, Williams & Wilkins Company, 1926. d'Herelle, F., and Rakieten, M. L.: Susceptibility of Hemolytic Staphylococci to Bacteriophage, J. A. M. A. **100**:1014 (April) 1933.

bacteriophage in clinical cases can be attacked there should be an appreciation of what this substance can be depended on to do under controlled optimum in vivo conditions. The plan of the investigation was to produce in an animal having tissue reactions similar to those of man a surgical infection with a bacterium against which there exists a specific bacteriophage of known and reliable virulence; to treat this infection with the lytic agent at varying intervals after its production, and to control each lesion thus treated with a similar, untreated infection.

Adolescent male dogs of the hound type, weighing from 18 to 20 pounds (8 to 9 Kg.), were used throughout the experiments. A hemolytic strain of Staphylococcus aureus was used as the infecting agent, and in order to simulate a well known and serious lesion in a human being as closely as possible, a suppurative arthritis of the knee joint was produced in the animals. Attempts were then made to protect the joints against the infection by the use of bacteriophage. Two purposes were thus served by the experiments: The effect of the bacteriophage was tested under controlled conditions, and at the same time there was tried a new and possibly useful adjunct in the therapy of suppurative arthritis, a disease for which the treatment has long been notoriously unsatisfactory.

REVIEW OF THE LITERATURE

A survey of the literature shows that no such work has previously been done. That a closed cavity of the body can be protected against infection by bacteriophage was shown by Zaytseff-Jern, Harvey and Meleney,[2] who were able to protect mice against peritonitis due to Bacillus coli by local treatments with bacteriophage up to three and one-half hours after the production of the lesion. Walker[3] has studied the effect of bacteriophage in experimentally produced cutaneous infections. No work has appeared, however, on this type of treatment in cases of artificial staphylococcic infections in the joints.

The susceptibility of the staphylococcus to the lytic action of bacteriophages was discovered soon after the phenomenon was described for the dysentery bacillus, and many potent races of phage have been developed which cause rapid and complete lysis of this organism in the test tube. Clinical applications of this fact have, however, in the main, met with disappointment. The type of lesion which has given the most

2. Zaytseff-Jern, H.; Harvey, H. D., and Meleney, F. L.: B. Coli Bacteriophage in the Treatment of B. Coli Peritonitis in Mice, Proc. Soc. Exper. Biol. & Med. **29**:741, 1932.

3. Walker, J. E.: Effect of Bacteriophage in Experimental Skin Infections, South. M. J. **24**:1087, 1931.

satisfactory results with bacteriophage therapy has been that of staphylococcic infections of the skin, Raiga,[4] Petit de la Villéon,[5] Zaytseff-Jern and others having obtained consistently good and often spectacular results in the treatment of furunculosis and carbuncles. MacNeal has reported a suggestive series of cases of staphylococcic septicemia in which the patients were treated by bacteriophage, and in which the mortality was very low for this disease. In the control of infections of surgical wounds bacteriophage has proved to be a disappointment. Several surgeons have tried this method of treatment in cases of osteomyelitis, one of the most dreaded of staphylococcic infections, but none has substantiated or even approached the glowing results reported by Albee,[6] who claimed to have been invariably successful with bacteriophage in the treatment of one hundred patients with osteomyelitis.

In 1931 there appeared in the French literature a remarkable series of reports[7] in which patients with suppurative arthritis were said to have been cured by injections of bacteriophage into the joint without other surgical or bacteriologic treatment. The enthusiasm of the authors reached a climax when Mirallié and Thiéry[8] claimed that staphylococcus bacteriophage had cured patients with streptococcic and gonorrheal arthritis, respectively. Grégoire[9] raised a voice against their case reports and reminded the authors that patients with arthritides due to these two organisms frequently get well without any treatment other than aspiration. No one else has deemed it necessary to controvert the claims of Mirallé and Thiéry.

Rice[10] reported success in the treatment with bacteriophage of many types of staphylococcic infections, including suppurative arthritis. We have used it, in one case of purulent arthritis of the knee as an adjunct to arthrotomy and drainage, without an encouraging result.

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4. Raiga, A.: Bacteriophage in Treatment of Furuncles and Carbuncles of the Face, Bull. et mém. Soc. d. chirurgiens de Paris **24**:571, 1932.

5. Petit de la Villéon: Staphylococcic Bacteriophage in Carbuncles and Furunculosis, Bull. et mém. Soc. de méd. de Paris **137**:68, 1933.

6. Albee, F. H.: The Treatment of Osteomyelitis by Bacteriophage, J. Bone & Joint Surg. **15**:58, 1933.

7. Wiart, P., and Mirallié, C.: Arthrite suppurée du genou guérie sans arthrotomie et avec un résultat fonctionnel excellent à la suite d'injections de bactériophage, Bull. et mém. Soc. nat. de chir. **57**:234, 1931.

8. Thiéry, P.: Sur le bactériophage, Bull. et mém. Soc. nat. de chir. **57**:655, 1931.

9. Grégoire, R.: A propos d'une arthrite suppurée du genou guérie sans arthrotomie à la suite d'injections de bactériophage, Bull. et mém. Soc. nat. de chir. **57**:477, 1931.

10. Rice, T. B.: Use of Bacteriophage Filtrates in Treatment of Suppurative Conditions, Am. J. M. Sc. **179**:345, 1930.

Larkum,[11] in 1932, gave the calmest and most rational evaluation of bacteriophage in clinical medicine that has yet appeared, and his conclusions are good up to the present. In one sentence he well summed up the danger to scientific medicine of unscientific writings: "So infinite are the possibilities which the discovery of this principle (bacteriophage) has made apparent that it would be nothing short of a calamity to have its continued investigation retarded or even halted through the unbridled enthusiasm of those who, without regard to the mechanism of its action, make use of this principle whenever an opportunity presents itself." This author drew attention to the fact, first brought out by d'Herelle,[1] that lysis is not the only means by which bacteriophage influences the relation between the host and the infecting bacterium; indeed, it may be of much less importance in that relation than the effect on phagocytosis, on the opsonins of the blood and on the virulence of the bacteria even when not lysed. Larkum stated that the proteins in the filtrate of bacteriophage resulting from the destruction of the bacteria probably are responsible for some of the beneficial results in the treatment, as they act as vaccines. Rice stated the belief that the success of local treatment of staphylococcic infections with bacteriophage is due to the combined action of the bacteriophage and antivirus. It is certain that, as Larkum said, "even without lysis, bacteriophage may considerably alter the course of an infection."

D'Herelle, Larkum, Applebaum and MacNeal,[12] Colvin,[13] Arnold and Weiss [14] and others have contributed much to the literature on the reasons for the failure of bacteriophage to produce lysis in the body of animals. The factors which are considered at present to be the chief inhibitors of this phenomenon in vivo are: (1) the inactivating influence of serum and exudates on bacteriophage, (2) the inhibition of bacteriophage by extracts of the bacteria and (3) the antigenic properties of bacteriophage, because of which inactivating antibodies are produced in the blood stream. Normal human blood serum is known to inhibit lysis in vitro. There is as yet no information on the influence of the fluid in the joints or of dogs' serum on lysis in the test tube.

There is considerable disagreement as to the importance of the serum antiphages in patients or animals treated with bacteriophage.

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11. Larkum, N. W.: Therapeutic Use of Bacteriophage, J. Lab. & Clin. Med. **17**:675, 1932.

12. Applebaum, M., and MacNeal, W. J.: Influence of Pus and Blood on the Action of Bacteriophage, J. Infect. Dis. **49**:225 (Sept.) 1931.

13. Colvin, M. G.: Behavior of Bacteriophage in Body Fluids and Exudates, J. Infect. Dis. **51**:527 (Nov.-Dec.) 1932; Relationship of Bacteriophage to Natural and Experimental Diseases of Laboratory Animals, ibid. **51**:17 (July-Aug.) 1932.

14. Arnold, L., and Weiss, E.: Antigenic Properties of Bacteriophage, J. Infect. Dis. **34**:317 (March) 1924.

Raiga, Gratia,[15] Sauvé [16] and others, especially those of the French school of bacteriologists, have stated the belief that the antiphages are of great importance, and they have gone to complicated lengths, such as the employing of autohemotherapy, to overcome their action. Larkum, Zaytseff-Jern and other American authors have come to consider them of very little clinical significance.

The literature on the subject of the treatment of acute suppurative arthritis was reviewed by one of us [17] in a recent paper. It is a disease of great seriousness and often of dire consequences, and the proper method for its surgical treatment is still a matter of dispute. It would indeed be a boon to the surgeon if bacteriophage therapy could be depended on as an adjunct to the surgical drainage of these severely damaged joints.

No references were found in the literature on the production of experimental suppurative arthritis in dogs. It is common knowledge that most of the laboratory animals have a high resistance to staphylococcic infections. This is especially true of the guinea-pig. Other animals, however, notably the rabbit, are extremely susceptible to lesions of the joints; Key [18] has produced the changes of chronic arthritis in this animal by the injection of many substances, even such bland ones as salt solutions and distilled water. The dog, coming between these two extremes and reacting more nearly like man to the staphylococcus, is therefore a more suitable animal for these experiments.

EXPERIMENTAL PROCEDURES

The first problem was the production of a satisfactory purulent arthritis. To determine the course of an untreated staphylococcic infection of a joint in the dog, a series of six of these animals was used. Into the suprapatellar pouch of the left knee, with aseptic technic, was inoculated an eight hour culture of a hemolytic strain of Staph. aureus in a meat infusion-peptone broth medium of p_H 7.8. It is realized that this procedure does not exactly simulate a hematogenous, embolic suppuration as it occurs in human synovial membrane, but the resemblancce is probably as close as that attained by many experimental surgical procedures and the process is as close to the pathogenesis of the human lesion as can be secured.

15. Gratia, A.: Le traitement des infections à staphylocoques par le bactériophage et les mycolysats staphylococciques, Bull. et mém. Soc. nat. de chir. **56**:345, 1930.

16. Sauvé, L.: A propos due bactériophage, Bull. et mém. Soc. nat. de chir. **56**:348, 1930.

17. Inge, G. A. L., and Liebolt, F. L.: The Treatment of Acute Suppurative Arthritis; Report of Thirty-Six Cases Treated by Operation, Surg., Gynec. & Obst. **60**:86 (Jan.) 1935.

18. Key, J. A.: Production of Chronic Arthritis by Injection of Weak Acids, Alkalies, Distilled Water, and Salt Solutions into Joints, J. Bone & Joint Surg. **15**:67, 1933.

The anatomy of the dog's knee joint is peculiar in that the extensor digitorum longus muscle arises by a tendon from the lateral condyle of the femur, traverses the joint and passes out of it distally through a well defined sheath, thus forming a communication between the cavity of the joint and the muscle compartments of the leg. In a few of the dogs the infection spread into the leg by this route.

So that we might find the most efficient pathogen, various strains of staphylococcus were tried in the experiments, and the dosage of bacteria was varied. "Staphylococcus C," for example, was a stock hemolytic strain of Staph. aureus which had been on agar slants for months, used in the propagation of bacteriophage, and "Staphylococcus F" was a recently isolated strain from a virulent infection of a wound.

SERIES I

The series consisted of six dogs. The left knee was infected; the right was left normal as a control. The dogs were killed at varying intervals after operation for autopsy studies.

Dog 3.—Three hundred million bacteria (Staph. C) in 3 cc. of broth were injected into the left suprapatellar pouch without anesthesia. There was slight pain from distention when the last cubic centimeter was injected. The dog did not limp immediately. Four hours later he was acutely ill; the knee was swollen, warm and tender and held rigid. The dog was apathetic and had no appetite. After three days the animal began to improve; he would stand and eat but always held the left foot off the floor. Distemper developed on the sixth day, and the dog was chloroformed on the ninth day. Roentgenograms of the knee showed effusion but no thinning of the joint space and no destruction of the bone. Culture of the knee showed nonhemolytic Staph. aureus.

At autopsy the right knee was found to be normal. The left knee was moderately swollen; when the joint was opened, 2 cc. of thin gray pus escaped. The synovial membrane was greatly thickened, injected and grayish red; it averaged 4 mm. in thickness. There were large synovial villi in the suprapatellar pouch and over the pad of patellar fat. Pus did not extend into the leg. The bone, auricular cartilage and menisci were normal.

Microscopic sections of the right knee showed a normal synovial membrane. Section of the left knee showed that this membrane was greatly thickened, being from 15 to 20 cells in thickness and edematous, with moderate formation of villi and erosion of the surface layers of the cells. The subsynovial tissues were thickened and edematous, and the blood vessels had increased in number and were injected. The synovial membrane and the subsynovial tissues were markedly infiltrated with polymorphonuclear leukocytes.

Dog 4.—Six hundred million bacteria (Staph. C.) in 3 cc. of broth were injected. Within a few hours severe arthritis developed, with hot, tense swelling, pain, tenderness and pitting edema in the leg from the knee to the ankle. There was a marked general reaction, with a hot, dry nose, apathy and loss of weight. The animal began to improve on about the tenth day, and on the twenty-first day some weight was borne on the affected leg, and the swelling and tenderness disappeared. Mild distemper was present from the fourteenth to the nineteenth day; the animal recovered. Aspiration of the knee on the twelfth and on the seventy-first day gave pure cultures of nonhemolytic Staph. aureus. The knee at times remained symptom-free and apparently normal; at other times, especially in bad weather, it became swollen, warm and painful. The dog was in good general health, and the knee was inflamed when he was killed with chloroform on the

ninety-first day after operation. Roentgenograms at this time showed swelling of the soft tissue and a slight thinning of the joint space, but no destruction of the bone. Culture of the knee at autopsy showed hemolytic Staph. aureus.

At autopsy the left knee showed about the same picture as that seen in dog 3, except that the process was much more marked, and in addition there were three areas of erosion of the articular cartilage, the largest of these being 4 mm. in diameter with erosion of the bone at the depth. The cruciate ligaments were covered with hypertrophied synovial membrane, and the menisci were yellowish but otherwise normal.

Microscopic sections showed marked proliferation of the synovial membrane and its infiltration with polymorphonuclear leukocytes and fibroblasts. The vessels were numerous, and there was some perivascular round cell infiltration in places. The subsynovial areolar tissue was hypervascular, with moderate polymorphonuclear infiltration. The staphylococcus recovered from this knee (now called Staph. D-4) was used as the infecting organism for all the dogs of series IV and V.

Dog 27.—Three hundred million bacteria (Staph. F) in 2 cc. of broth were injected. This amount of broth caused no distention and no pain. Moderately severe arthritis developed which persisted until the dog's death from distemper on the eleventh day after operation. Culture yielded hemolytic Staph. aureus.

Autopsy showed a slight serosanguineous exudate and a slightly thickened synovial membrane which was quite injected. The articular cartilage was intact but showed several areas of purplish-red discoloration.

Microscopic sections showed moderate proliferation of the synovial membrane averaging from 12 to 15 cells in thickness, marked infiltration with leukocytes and extensive erosion of the surface layers.

Dog 28.—This dog received the same injection as dog 27. Clinically the condition was moderately severe arthritis without much general reaction, from which the dog completely recovered by the twenty-first day. The injection was repeated on the sixty-seventh day, causing mild transient arthritis which lasted seven days. On the ninetieth day after the original operation the animal was given an injection into each knee; mild acute arthritis developed, lasting six days on the left side and fifteen on the right side, with no general reaction. The animal was killed with chloroform on the one hundred and twenty-third day (thirty-three days after the last injections). Cultures of both knees showed nonhemolytic Staph. aureus.

At autopsy both joints appeared practically normal except for slight redness between the femoral condyles.

Microscopic sections showed very slight thickening of the left synovial membrane and an occasional leukocyte; the right knee was normal. This dog was obviously very highly resistant to the staphylococcus.

Dog 29.—Six hundred million bacteria (Staph. F) in 2 cc. of broth caused a moderately severe lesion with a slight general reaction, from which the dog recovered in five weeks. On the sixty-seventh day after operation an injection of one million bacteria (Staph. 1968) was given into the same knee. This caused only slight arthritis with little general reaction, from which the dog recovered in one week. He was killed on the one hundred and twenty-fourth day after the first, and fifty-seven days after the second, injection. Roentgenograms showed no pathologic condition. Culture of the left knee showed no growth after seventy-two hours.

Microscopic sections showed moderate thickening of the synovial membrane and a very light leukocytic infiltration; there were no polymorphonuclears in the subsynovial tissue. Grossly the joint showed little abnormality, there being slight synovial thickening and some superficial erosion of the articular cartilage on the femoral condyles.

Dog 30.—Six hundred million bacteria (Staph. F) in 2 cc. of broth were injected. Moderately severe acute arthritis occurred, which, however, cleared up spontaneously by the thirteenth day. There was no general reaction. The animal was killed with chloroform because of distemper on the sixteenth day. Roentgenograms showed no pathologic condition, and the culture showed no growth after seventy-two hours. Grossly and microscopically the joint appeared to be normal. This was a case of transient acute arthritis in a dog with a very high resistance.

Summary.—Of six dogs infected there were one with a severe, three with a moderate and two with a mild infection. One dog with a mild infection had received repeated injections of bacteria. The dose apparently played no part in the variation, since the severest and the mildest infection were caused by the same dose. Evidently there is a great variation among dogs of the same sex, size and age in their resistance to staphylococcic infections. Untreated staphylococcic purulent arthritis in the dog seemed to be no great threat against life and even in the severest case tended to subside spontaneously, leaving more or less structural damage but never any great disorganization of the joint or impairment of its function.

SERIES II

Having determined that purulent arthritis could be produced, we next proposed to determine the effect of repeated injections of bacteriophage alone into normal joints and of broth alone into control joints. Such a norm had to be established before accurate interpretations could be made of the treated knees in the later series. For this purpose four dogs were used. The broth was the same as that used in the bacterial cultures; the phages were the filtrates from completely lysed cultures of Staph. aureus in broth, after they had been passed through Chamberland L 3 filters and tested for potency in vitro. Two potent races of phage were used, one (B L S) having been obtained indirectly from Dr. A. Gratia of Brussels, the other (B 5 9 A) indirectly from Dr. N. W. Larkum of Michigan.

Dog 1.—Three cubic centimeters of B L S bacteriophage was injected into the left knee joint. Three cubic centimeters of broth was injected into the right knee joint. There was no early or late evidence of pain in the joints. On the seventh day both injections were repeated, but 2 cc. was used. No evidence of arthritis developed. The dog was killed with chloroform on the twentieth day because of distemper. Roentgenograms showed no pathologic condition. No bacteriophage was recovered from the left knee. Autopsy revealed two grossly normal joints. Sections were unsatisfactory, and the condition of the synovial membrane could not be judged.

Dog 2.—This dog was given the same injections as those first employed for dog 1. Except for slight distention with the injections there were no symptoms or signs of arthritis in either knee. The injections were repeated at about nine day intervals for ninety days, a total of ten injections being made into each knee.

There were no symptoms following the first six injections; the fluid was quickly absorbed. After the eighth injection after operation the dog limped on his left leg for a few hours. The dog's general health was unaffected until it was killed on the ninetieth day. Roentgenograms at this time showed no pathologic condition. Cultures showed no growth, and no bacteriophage was recovered from the left knee. At autopsy the right knee showed no excess fluid, but there was a slight injection of synovial membrane around the patellar pad of fat; the left knee contained a few drops of serous fluid, and the membrane was slightly thickened and injected throughout. Sections showed a normal synovial membrane on the right; on the left, there were slight proliferation of the synovial layer, increased formation of villi and patchy infiltration with leukocytes. The subsynovial tissues were normal.

Dog 287.—An injection of 8 cc. of B 5 9 A bacteriophage was made into the left knee, the joint being distinctly distended; light ether anesthesia was used. One hour later an attempt was made to aspirate some of this phage to test its potency after it had come into contact with the fluid of the joint and the tissues. All the fluid had been absorbed by that time, and none could be aspirated. The dog showed no evidence of arthritis. The injection was repeated four days later, the aspiration being done thirty minutes after injection; most of the fluid had been absorbed, so that only a few drops were recovered. This fluid, when tested against a fresh culture of staphylococci, showed no lytic action. The dog showed no evidence of arthritis; he died of distemper on the eleventh day; the body was destroyed by mistake, so that no autopsy was performed.

Dog 288.—An injection of 8 cc. of B 5 9 A bacteriophage was made into the left knee under light ether anesthesia. Thirty minutes later distention had disappeared; no fluid could be aspirated. The injection was repeated two days later; after fifteen minutes aspiration yielded 0.5 cc. of blood-tinged fluid which caused partial lysis of a culture of staphylococci in vitro and a few plaques when plated on agar. A third injection was given three days later, and aspiration after five minutes yielded about 1 cc. of fluid which caused three plus lysis in the test tube and showed numerous plaques on agar. The dog showed no evidence of arthritis at any time. Autopsy was not performed.

Summary.—Four dogs were used as a control series to determine the effect of bacteriophage alone and of plain broth alone on a normal joint. Of four joints into which injections of bacteriophage had been made, only one showed arthritis, and this was of mild degree following ten injections. The two knees into which sterile broth was repeatedly injected showed no evidence of arthritis clinically or at autopsy. When attempts were made to aspirate bacteriophage from the knee, it was found that the fluid was rapidly absorbed; when fluid was recovered, after being in the joint for thirty minutes, it had entirely lost its lytic action, and after being in contact with the interior of the joint for fifteen minutes it was only weakly active, in spite of the fact that it was of high virulence when injected.

SERIES III

In this series of four dogs suppurative arthritis was produced in the knee by the technic used in series I and the lesion treated at various intervals by the injection of bacteriophage. Because of the wide variation in the susceptibility of

individual dogs to staphylococcic infection, as shown in series I, it was decided that each dog must furnish his own control for the treated joint; therefore, both knees of each animal were simultaneously given injections of equal numbers of staphylococci. One of the knees (the left) was then treated with bacteriophage, the other remaining untreated as a control. In this manner the error due to individual reactions was largely eliminated, but care had to be taken not to kill the dog with too great an infection.

Dog 79.—An injection of 300,000,000 bacteria (Staph. F) was made into each knee without anesthesia. Twenty-four hours later there was severe arthritis in both knees, with a moderate general reaction; the left knee received 2 cc. of bacteriophage. This treatment was repeated every two days, the dose ranging from 0.5 to 2 cc., depending on the amount of distention present in the joint; six treatments, a total of 8.5 cc., were given. The treated knee presented clinically and at autopsy acute purulent arthritis just as severe or perhaps a little worse than that shown by the control knee. Roentgenograms taken before autopsy was performed showed equal swelling of the soft tissue in the two knees, and the pathologic symptoms were grossly and microscopically about the same on the two sides. Cultures of the right knee showed nonhemolytic Staph. aureus; those of the left knee, the same organism, plus the presence of a weak bacteriophage. The dog was killed on the thirteenth day.

Dog 80.—Three hundred million bacteria (Staph. F) in 1.5 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. F) suspended in 1.5 cc. of B 5 9 A bacteriophage, into the left knee. In both joints there developed moderately severe arthritis, of the same degree on each side. The left knee then received twelve injections of bacteriophage at forty-eight hour intervals, the doses varying as for dog 79. Both lesions began to subside on about the fourteenth day, and there was no difference between the two joints either clinically or at autopsy. Sections showed the same degree of pathologic change in each knee. Cultures of both knees showed nonhemolytic Staph. aureus, and no bacteriophage was recovered from the left knee at autopsy. The dog was killed on the thirty-fifth day.

Dog 81.—This animal was given the same injections as dog 80. He was treated with thirteen injections of bacteriophage in the left knee over a period of twenty-three days. Clinically and by gross and microscopic examination at autopsy the treated left knee presented much more severe arthritis than did the right knee. Cultures of both knees at autopsy gave no growth.

Dog 82.—This dog was given the same injections as dog 79. The first operation consisted in the injection of bacteria only. Treatment of the left knee began after twenty-four hours. Thirteen injections of bacteriophage were given in twenty-three days. Clinically and at autopsy the treated left knee showed the more severe arthritis. Cultures of both knees showed no growth.

Summary.—In four dogs suppurative arthritis was produced in both knees. In two dogs the left knee was treated with bacteriophage simultaneously with the bacterial inoculation; in the others the first treatment with bacteriophage was given twenty-four hours after the bacterial inoculation. In all four dogs the treatment with bacteriophage was repeated every forty-eight hours until the animal was killed. In one dog there was not much difference between the two joints clinically or at autopsy, and in the other three dogs the treated knee was more severely damaged than the control knee.

SERIES IV

Because of the aforementioned results, all attempts to treat the knees after the infection had become well established were given up, and it was decided that the first determination to be made was whether bacteriophage injected simultaneously with bacteria could protect a joint against infection. Since it was possible that the repeated injections of phage were the cause of more damage to the joint by trauma from the distention, it was also decided that in this series only one treatment with phage would be given and that simultaneously with the bacteria. In all the animals of this series the strain of staphylococcus used was Staph. D-4, a hemolytic organism which was recovered from the knee of dog 4, series I. The bacteriophage used was B 5 9 A.

Dog 116.—Three hundred million bacteria (Staph. D-4) in 1 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. D-4) in 1 cc. of B 5 9 A bacteriophage, in the left knee. Acute arthritis of moderate severity developed in both knees; it was slightly worse in the left knee clinically and subsided in both knees on about the eighth day. The animal was killed on the eleventh day. Autopsy showed changes of moderate acute synovitis equal in the two knees. Roentgenograms taken before autopsy was performed showed no abnormalities, and cultures of both knees remained sterile.

Dog 117.—This dog was given the same injections as dog 116. Severe arthritis developed in both joints, with a marked general reaction. Clinically and pathologically the left knee was less severely damaged than the right. The latter contained 3 cc. of pus from which nonhemolytic Staph. aureus was cultured; the left contained 1 cc. of serous fluid which was sterile but contained no demonstrable bacteriophage. Autopsy was performed on the eighth day.

Dog 118.—This dog was given the same injections as dog 116. Severe arthritis, clinically about the same on the two sides, was present. The dog died twenty-four hours after operation, probably of an embolus. At autopsy the treated knee was less severely damaged than the control. The right knee contained 3 cc. of thin gray pus which yielded hemolytic Staph. aureus; the left knee contained 3 cc. of serosanguineous exudate which was sterile and from which no bacteriophage was recovered.

Dog 119.—This dog was given the same injections as dog 116. Clinically and pathologically the treated joint was less damaged than the control joint. At autopsy on the eighteenth day the treated knee was almost normal; severe arthritis developed in the right knee. Culture of the right knee yielded hemolytic Staph. aureus and a hemolytic streptococcus (contamination?); culture of the left knee yielded no growth, and no phage was recovered.

Dog 88.—This dog was given the same injections as dog 116. Arthritis of moderate degree developed, lasting only twelve days in the right and eleven days in the left knee. Clinically and pathologically the treated knee was slightly worse than the control. Culture of both knees yielded nonhemolytic Staph. aureus. No bacteriophage was recovered from the left knee. The animal was killed on the twenty-second day.

Dog 108.—This animal was given the same injections as dog 116. There was severe arthritis in both knees, persisting up to death on the twenty-eighth day after operation. Neither clinically nor pathologically was there any difference between the two joints. Culture of both knees yielded hemolytic Staph. aureus; no bacteriophage was recovered from the left knee.

Dog 112.—This animal was given the same injections as dog 116. There was a moderately severe lesions, of equal degree in the two knees, subsiding on about the twentieth day after operation. In both knees the pus burrowed into the leg along the tendon of the extensor digitorum longus muscle. Autopsy on the thirty-second day showed that the two joints were about the same. Cultures of both knees remained sterile. This dog was a female, the only one used in the entire series.

Dog 122.—This animal was given the same injection as dog 116. There was a severe lesion in both knees, with a marked general reaction. Clinically and pathologically the treated knee appeared less damaged, though at autopsy severe synovitis was found in both joints. The organism was recovered from the right knee; culture of the left knee was sterile, with no demonstrable bacteriophage. The dog was killed on the fifteenth day.

Dog 123.—Three hundred million bacteria (Staph. D-4) in 1 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. D-4) in 1 cc. of B 5 9 A-4 bacteriophage (a specific phage, prepared with Staph. D-4 instead of with stock strains) were injected into the left knee. The right knee showed severe acute arthritis persisting until the animal was killed with chloroform on the eighteenth day. The left knee showed moderate arthritis, which had subsided by the eighth day. At autopsy there was a marked difference between the two joints in favor of the treated side. Culture of the right knee yielded hemolytic Staph. aureus; that of the left knee yielded no growth, and no phage was recovered.

Dog 124.—This animal was given the same injections as dog 123. A severe lesion with marked constitutional symptoms developed in both knees; it began to subside on about the thirteenth day after operation. Clincally and at autopsy the treated knee was more severely affected than the control. The dog was killed with chloroform on the twenty-first day. Culture of both knees yielded nonhemolytic Staph. aureus.

Dog 125.—This animal was given the same injections as dog 123. Moderately severe lesions developed which persisted until death from chloroform on the twentieth day, with a moderate general reaction. Clinically and at autopsy there was less damage to the treated knee than to the control. A slight amount of serous fluid was present in each knee, which on culture remained sterile.

Dog 126.—Injections were given as for dog 123. Severe acute suppurative arthritis persisted in the right knee with death on the twenty-first day, autopsy showing a badly inflamed joint with pus which yielded hemolytic Staph. aureus. A much less severe clinical infection developed in the left knee, which showed at autopsy only mild synovitis with some serous fluid from which the organism was recovered; the condition in the left knee subsided clinically by the thirteenth day.

Dog 133.—Injections were given as for dog 123. In the right knee a severe lesion developed which persisted until death on the fifth day; there was 3 cc. of pus in the joint, and marked synovitis was observed at necropsy. In the left knee distinct but less severe synovitis developed; there was no pus in the joint when it was opened. The dog walked on this leg on the fourth day. Culture of both knees revealed nonhemolytic Staph. aureus.

Dog 134.—Injections were given as for dog 123 except that in the right (control) knee some of the injected fluid penetrated into the subcutaneous tissues instead of into the joint. The dog became very ill, and a severe inflammatory reaction developed in both knees. Clinically and by gross and microscopic examination at autopsy the left (treated) knee was more severely damaged than the control. The organism was recovered from both joints. The animal was killed on the fifth day.

Dog 135.—Injections were given as for dog 123. Moderately severe arthritis developed, which clinically and at autopsy was worse on the treated side. Culture

of the treated left knee yielded nonhemolytic Staph. aureus; culture of the right knee showed no growth after seventy-two hours. The dog was killed on the seventh day.

Dog 136.—Injections were made as for dog 123. The dog became very ill; a severe lesion developed in both knees, the lesion in the left being more severe. At autopsy on the ninth day the right (control) knee contained 2 cc. of pus; the left knee contained 5 cc. in the joint and 15 cc. in an abscess which had burrowed into the leg. The organism was recovered from both knees.

Summary.—In sixteen dogs the right knee was given an injection of 300,000,000 staphylococci suspended in broth, and the left knee simultaneously received an injection of the same number of bacteria suspended in bacteriophage. In every control knee there developed well marked suppurative arthritis; in no case did the bacteriophage completely protect the left knee against the formation of arthritis, but in eight (50 per cent) of the dogs the treated knee showed less severe damage than the control. In two dogs the knees were damaged equally, and in six the treated knee was worse, clinically or pathologically or both, than the control. Culture of the control knee was positive for Staph. aureus in twelve cases and sterile in four; eight cultures of the left, or treated, knees yielded Staph. aureus, and eight were sterile. In none of the treated knees could bacteriophage be recovered at autopsy. In four controls and four treated knees the staphylococcus recovered at autopsy had lost its hemolytic power. The sixteen experiments of this series were allowed to run for varying lengths of time from one to thirty-two days. The effect of the bacteriophage did not seem to vary consistently with the duration of the infection. In this series, no bacteriophage treatments were given after the original injections.

Table 1 shows the results of this series in condensed form:

TABLE 1.—*Results of Experiments in Series IV*

Dog	Duration of Experiment, Days	Condition of Treated Joint Compared with Control	Culture of Treated Knee at Autopsy	Culture of Control Knee	Serum Antiphage
116	11	Worse	Negative	Negative	Strong
117	8	Better	Negative	Positive	Weak
118	1	Slightly better	Negative	Positive	Strong
119	18	Better	Negative	Positive	Strong
88	22	Worse	Positive	Positive	Moderate
108	28	Same	Positive	Positive	Moderate
112	32	Same	Negative	Negative	Moderate
122	15	Slightly better	Negative	Positive	Moderate
123	18	Better	Negative	Positive	Strong
124	21	Worse	Positive	Positive	Strong
125	20	Slightly better	Negative	Negative	Strong
126	21	Better	Positive	Positive	Strong
133	5	Better	Positive	Positive	Weak
134	5	Worse	Positive	Positive	Weak
135	7	Worse	Positive	Negative	Moderate
136	9	Worse	Positive	Positive	Weak

These results were not encouraging. The bacteriophage used for the aforementioned animals, although causing four plus lysis grossly

in tubes of broth, often showed a few colonies of staphylococci when plated on agar before filtration. It was therefore possible that the poor results were due to less than maximum potency of the bacteriophage. The method of preparation of the phage was therefore changed, and the method employed by the d'Herelle Laboratory in Paris was adopted. The same strain of staphylococcus and the same race of bacteriophage were continued. This method of preparation resulted in a phage of maximum potency which not only gave four plus lysis in broth tubes but showed no growth on agar plates before filtration. Any lot failing to meet these specifications was discarded. With this new phage of maximum potency it was decided to repeat the experiment on a short series of dogs.

SERIES V

Four dogs were given injections similar to those used for series IV, but a bacteriophage of greater potency was employed.

Dog 220.—Three hundred million bacteria (Staph. D-4) in 1 cc. of broth were injected into the right knee, and 300,000,000 bacteria (Staph. D-4) in 1 cc. of bacteriophage into the left knee. Severe arthritis developed in both knees, perhaps slightly less severe in the treated knee clinically and at autopsy. On both sides the abscess extended into the leg along the tendon of the extensor digitorum muscle. Culture of both knees yielded hemolytic Staph. aureus. The dog was severely ill and was killed with chloroform on the eighth day.

Dog 221.—Injections were made as for dog 220. A moderately severe lesion developed which was clinically about the same on each side but at autopsy much worse in the treated left knee. The animal was killed on the seventh day. Cultures of the right knee yielded nonhemolytic Staph. aureus; that of the left knee, large gram-positive bacilli (contamination).

Dog 222.—Injections were made as for dog 220. A fairly severe lesion developed in both knees; clinically it was about equal in the two knees, but at autopsy the treated knee showed less damage than the control. The animal was killed with chloroform after forty-eight hours. The organism was recovered from both knees.

Dog 223.—Injections were made as for dog 220. Very mild and transient arthritis developed, from which the dog recovered on the fourth day. On the sixth day distemper developed. The animal was killed with chloroform on the seventh day. At autopsy the control knee showed very little change from the normal, whereas the left knee presented a well defined purulent synovitis. Cultures of the right knee showed no growth; that of the left knee, nonhemolytic Staph. aureus and gram-positive bacilli.

Summary.—In two of four dogs, the treated knee was less severely damaged than the control, and in two it was more severely damaged—about the same percentage as in series IV.

Apparently, therefore, it is not the impotence of the bacteriophage which accounts for the failure of the treatments, and one is forced to the conclusion that in a closed synovial cavity this substance will not protect against infection, even though the bacteria are completely

susceptible to the phage in vitro and though the phage is injected into the joint simultaneously with the bacteria. Obviously there was no use of conducting further experiments in which conditions would more nearly approach human clinical conditions. However, as a matter of theoretical interest it was decided to try the effect of injecting a bacteria-bacteriophage mixture into dogs' knees at varying lengths of time after the bacteria and bacteriophage had been in contact in the test tube at 37 C., thus allowing time for the fixation of the bacteriophage corpuscles by the bacteria (if that is the mechanism of bacteriophagy).

SERIES VI

Four dogs were used. The right knee was used as a control, and no anesthesia was used. The bacteria were from an eighteen hour agar slant of Staph. D-220 (recovered from the right knee of dog 220, series V), washed down with 1 cc. of broth; 2 drops of this heavy suspension was then added to 8 cc. of broth, giving a turbidity of 500,000,000 bacteria per cubic centimeter. This suspension was then divided, half being used for the control injections and the other half mixed with 0.2 cc. of bacteriophage, incubated and used for injections into the left knee.

Dog 248.—Two hundred and fifty million bacteria (Staph. D-220) in 0.5 cc. of broth were injected into the right knee, and 0.5 cc. of the bacteria-bacteriophage mixture (also containing 250,000,000 bacteria [Staph. D-220]) after twenty-five minutes' incubation, into the left knee. Moderately severe arthritis developed in both joints, but the left knee was slightly less damaged than the control both clinically and pathologically. The dog was killed on the seventh day. The condition in both knees was subsiding at that time. Cultures of both joints yielded nonhemolytic Staph. aureus, that of the left knee showing no contamination with bacteriophage.

Dog 249.—Injections were made as for dog 248, the bacteria-bacteriophage mixture having been incubated for twenty minutes. The left knee was clinically and pathologically much more damaged than the right, which showed very little inflammation at autopsy. Culture of the right knee showed no growth; that of the left showed nonhemolytic Staph. aureus not contaminated with phage. The animal was killed on the ninth day.

Dog 250.—Injections were made as for dog 248, the bacteria-bacteriophage mixture having been incubated for thirty-four minutes before injection. A severe bilateral lesion with marked general reaction developed. Clinically and at autopsy one knee was as bad as the other. The organism was recovered from both joints when they were opened on the seventh day.

Dog 251.—Injections were made as for dog 248, but after thirty-eight minutes' incubation. The dog showed no reaction to the inoculations, and no arthritis developed in either knee. The animal was saved for use in another experiment. There was no autopsy.

Summary.—Of four dogs which received injections as described, one showed a high resistance, and no arthritis developed in either knee; in one the treated knee was less damaged than the control; in another it was more damaged than the control, and in the fourth animal no difference could be seen between the two joints either clinically or

at autopsy. Apparently thirty minutes is not enough time for the "fixation" of staphylococci by the virulent bacteriophage. The organism was recovered from the left knee in all three cases in which cultures were taken, and in the case of one control knee the culture yielded no organism. Table 2 shows briefly the results of the experiments in series V and VI:

TABLE 2.—*Results of Experiments in Series V and VI*

Dog	Duration of Experiment, Days	Condition of Treated Joint Compared with Control	Culture of Treated Knee at Autopsy	Culture of Control Knee
220	8	Better	Positive	Positive
221	7	Worse	Contaminated	Positive
222	2	Slightly better	Positive	Positive
223	7	Worse	Positive	Negative
248	7	Better	Positive	Positive
249	9	Worse	Positive	Negative
250	7	Same	Positive	Positive
251	No arthritis developed		No cultures taken	

COMMENT

Variation in the Resistance to Infection.—Human synovial membrane is known to have considerable resistance to infection. It is natural to expect this tissue in the dog to show the same property, and it would be unusual if there were not individual variations in the degree of this resistance. As a species, however, it is certain that this animal is less susceptible to staphylococcic infections than is man. That it is not the dog's serum which alone is responsible for this is suggested by the fact that the serum of all dogs of series I, III and IV (twenty-four dogs) was tested for its power to inhibit the growth of the staphylococcus used in the particular experiment, and in no case was there failure of the bacteria to grow in the tube containing the serum as well as, or better than, in the control tube of plain broth. In vitro, at least, therefore, the dog's serum cannot explain the variations in the resistance to infection which were noted. The complication of distemper seemed also to have no effect on the resistance to the infection of the joint. All the dogs were healthy before the experiments began, and it was found to be impossible to predict which dogs would be most susceptible.

Response of the Normal Joint to Injections of Broth and of Bacteriophage.—It was apparent from the results in series II, when the pathologic condition of each knee was judged at autopsy, that the effect of broth and of bacteriophage alone in the joints could be ignored. Only in the treated knees of the dogs of series III could these factors have played any part, and in those it was probably the trauma from repeated distention by the treatments with bacteriophage which caused the joints to be more damaged than the controls.

Results of Treatments.—Each time an injection of staphylococci and bacteriophage was made, a similar mixture of the same materials was incubated in the test tube as a control. In every instance the control in vitro showed complete lysis, whereas in the animal's knee no such lysis could have taken place, as was shown by the development of a more or less severe purpulent arthritis in every case. Why does this striking difference in behavior occur? The complete discussion of the problem is beyond the scope of this paper, but there are two factors which should be considered: the effect of joint fluid and the effect of serum on bacteriophagy.

It was noted in the cases of dogs 287 and 288, series II, that large injections of bacteriophage into the knee were rapidly absorbed and that when some of the fluid could be recovered by aspiration it was found to have lost, or nearly lost, its lytic action after a relatively short period of contact with the interior of the joint. As normal fluid from the joint could not be obtained in quantities large enough to test in vitro, this was the only method available for determining the effect of joint fluid on the action of bacteriophage. Unfortunately, it is not a satisfactory method, since the phage comes into contact with several things in addition to the joint fluid. The fact that the aspirated fluid showed no lytic action or a very weak one suggests that the bacteriophage, injected simultaneously with the bacteria, was quickly inactivated by the joint fluid or the exudate or both, in the experimental joints, thus leaving the bacteria to wreak their havoc almost unhindered. Whatever the effect of bacteriophage on bacteria in vivo, whether lysis or some other attribute is the chief factor in this effect, the inactivation by the fluids of the body exerts the same inhibiting influence.

The Question of Serum Antiphages.—The serum of twenty-four of these dogs was tested for the presence of the staphylococcus antiphage before any experimental work was begun on them. It was not considered necessary to test for the streptococcus antiphage. The term "antiphage" in this connection is misleading, since it suggests an antibody produced in the blood stream in response to the presence of an antigen; in these young dogs which had never received bacteriophage and in which there had never been an infection in which spontaneous staphylococcus phages might have appeared, there is obviously no reason to expect the presence of an antibody to bacteriophage, or antiphage. The fact that dog 2, series II, showed no increase in the strength of his serum "antiphage" after ten injections of bacteriophage over a period of ninety days strongly suggests that "serum antiphage" is simply the inhibiting action of normal serum. Nevertheless, "antiphage" tests were done on twenty-four dogs, both by the Rosenthal method and by a method used by Zaytseff-Jern, in which two tubes are set up, one, the control, containing bacteria plus bacteriophage in broth, and the

other containing the same amount of bacteria and phage with the addition of 2 drops of the serum to be tested. The latter method approaches much more nearly to in vivo conditions than does the Rosenthal test, direct or indirect. The results of the antiphage tests are shown in table 3. Unless otherwise stated, serums were not more than twenty-four hours old when tested.

TABLE 3.—*Results of the Antiphage Tests for Various Dogs*

Dog	Antiphage by Method of Zaytseff-Jern	Antiphage by Method of Rosenthal	
		Direct	Indirect
1	Strong	Moderate	Strong
2	Moderate	Weak	Weak
3	Very strong	Strong	Strong
4	Moderate	Strong	Weak
990*	Moderate	Strong	Weak
79	Very strong	Moderate	Weak
80	Very strong	Moderate	Weak
81†	Very strong	Absent	Absent
82	Very strong	Moderate	Weak
116	Very strong	Strong	Moderate
118	Very strong	Strong	Strong
119	Very strong	Strong	Strong
88	Moderate	Strong	Weak
108	Moderate	Strong	Moderate
112	Moderate	Strong	Moderate
122	Moderate	Strong	Weak
123	Very strong	Very strong	Very strong
124	Strong	Very strong	Strong
125	Very strong	Very strong	Strong
126	Very strong	Very strong	Strong
133	Moderate	Strong	Weak
134	Weak	Very strong	Weak
135	Moderate	Very strong	Weak
136	Weak	Strong	Weak

* This dog not used in the experiments.
† This serum was four days old when tested.

Table 3 is especially interesting when compared with table 1, which shows the results of treatment in the dogs of series IV. It is obvious that the results of the treatments do not coincide with the strength of the animal's antiphage; of seven dogs with strong antiphage reactions, five showed improvement in the treated knee, while two showed exacerbation of the infection in the treated knee; in four dogs with weak antiphage, the treated knee was better than the control in two and worse than the control in two. These results are consistent with those observed in human patients by numerous observers, namely, that the best results of treatment are often seen in patients showing the strongest antiphage reactions. Because of this, antiphage tests were not carried out on the animals of series V and VI, and no attempts were made to influence the effect of bacteriophage by such procedures as autohemotherapy.

Pathology.—The results of the experiments were judged for the most part by the clinical picture and the gross pathologic appearance of the joints at autopsy. Microscopic sections were made of all the knees except four. It was usually possible to tell the character, but not

the extent, of the infection from these sections. In the majority of the knees the inflammatory reaction was an acute one, with more or less leukocytic infiltration, edema and fibroblastic organization. In quite a few of the knees, however, notably in dogs 80, 81, 108, 116, 123 and 124, the infiltration of the synovial membrane and subsynovial tissues was more of the chronic inflammatory type, the cells being mostly plasma cells, large wandering cells and lymphocytes. Some of the areas in these sections had an appearance quite similar to that seen in human chronic proliferative synovitis. The not infrequent perivascular grouping of the plasma cells and the lymphocytes formed pictures not greatly unlike those of the Aschoff bodies in rheumatic fever. It was found, as might be expected, that the chronic type of inflammatory reaction was seen in the sections from the dogs in which the infection had more or less subsided before autopsy.

Bacteriology.—The failure to recover the organism from several control knees can be attributed to the culture medium in two cases of series IV; a check-up of the hydrogen ion concentration of the broth showed that one lot which was being used was too alkaline. In a few other cases it may have been due to the fact that the specimens lay in the refrigerator for twenty-four hours before section and culture. The technic of taking the cultures was the same in all cases. The fact that the bacteriophage was not often recovered from the treated knee at autopsy is not surprising after the results of the experiments in dogs 287 and 288. This test was not made in all the treated knees, and in the two cases in which a weak phage was demonstrated this phage was not built up to its original potency. Perhaps if this had been done, a bacteriophage more appropriate for infections of the joints could have been produced. Further research is necessary along this line.

The frequent loss of hemolytic power by the staphylococcus after it had remained in some of the joints was interesting. That the bacteriophage had nothing to do with this loss of power is shown by the fact that it usually occurred in both knees of the same animal and also that it occurred in some of the dogs of series I which received no bacteriophage. There was no consistent relation between the hemolytic power of the organism and the severity of the infection or between the hemolytic power of the organism and the effect of the treatments with the bacteriophage.

SUMMARY AND CONCLUSIONS

The literature was reviewed and no work found on the experimental use of bacteriophage in infections of the joints.

In order to test this biologic principle under controlled conditions, six series of dogs were used: series I, consisting of six dogs in which suppurative arthritis of the knee was produced and left untreated to

determine the course of the disease; series II, consisting of four dogs in which the effect of repeated injections of bacteriophage alone and of broth alone were studied; series III, consisting of four dogs in which purulent arthritis was produced in both knees with subsequent repeated injections of bacteriophage into the left knee, the right remaining as a control; series IV, consisting of sixteen dogs, into the right knee of which bacteria suspended in broth were injected and into the left knee of which the same dose of bacteria suspended in bacteriophage was injected; no subsequent bacteriophage treatments were given; series V, consisting of four dogs treated as in series IV but with a more potent bacteriophage; series VI, consisting of four dogs into the left knee of which was injected a bacteria-bacteriophage mixture incubated for varying lengths of time before the injections were made. Bacteria alone were injected into the right knee as a control.

It is believed that the foregoing experiments are sufficient in the number of dogs used and in the fairly consistent results to establish the following facts:

1. Acute suppurative arthritis can be produced in the dog's knee with the staphylococcus, the lesion showing a tendency to subside spontaneously and the duration of the infection varying in different dogs.

2. Repeated injections of bacteriophage alone into the knee joint of a normal dog are not without some danger of the formation of mild acute synovitis.

3. Repeated injections of broth alone into the normal knee cause no such arthritis.

4. Bacteriophage is useless as the sole means of protecting a joint against a closed suppurative arthritis.

5. The failure of bacteriophage to act in such a situation is due to complicated biologic reactions which are not elucidated by this series of experiments but which are probably in great part related to the inactivation of bacteriophage by body fluids.

6. The presence of serum "antiphage" does not exert any deleterious influence on the outcome of such experiments.

Future research must either develop a bacteriophage which will not be inactivated by body fluids and exudates or find a method of treating the body so as to render its fluids innocuous to the bacteriophage. The latter problem has been attacked with partial success by the use of autohemotherapy; the former probably offers the more fruitful field for investigation.

EFFECT OF DIET ON WEIGHT OF LIVER AND GLYCOGEN CONCENTRATION IN PARTIALLY HEPATECTOMIZED RATS

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Experimental approaches to the study of the physiology of the damaged liver have been made by (1) the use of hepatic poisons, (2) ligation of the radicles to a lobe of the liver, (3) a reduction of hepatic substance after diversion of the portal blood through an Eck fistula and (4) partial hepatectomy. The most practicable experimental approach to the problem would appear to be the last of these procedures, because of the fact that only by this method can damage to the liver in experimental animals and in controls be approximately comparable. In animals subjected to partial hepatectomy two indexes which may be used for studying the function of the damaged liver are regeneration of the liver and storage of glycogen. In addition, the general effect of damage to the liver may be observed by studying the curve for body weight

The present investigation in the field of the physiology of the damaged liver has employed the method of partial hepatectomy and has been limited to a study of the effects of various diets on the experimental animals. The results of this investigation offer a certain possibility of reference to the clinical problem of the patient with presumable diminution of hepatic function.

REVIEW OF THE LITERATURE

Regeneration of the Liver.—After the removal of 75 per cent of the liver of dogs von Meister [1] and Mann and Magath [2] noted that the liver was restored to 80 per cent of its original weight in a period of about eight weeks. Fishbach [3] confirmed this observation and, in addition, presented a morphologic study of the regenerating liver. Higgins

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1. von Meister, V., quoted by Fishbach.[3]

2. Mann, F. C., and Magath, T. B.: Am. J. Physiol. **59**:485, 1922.

3. Fishbach, F. G.: A Morphological Study of Regeneration of the Liver After Partial Removal, Arch. Path. **7**:955 (June) 1929.

and Anderson [4] were the first to report the regeneration of liver in the rat after partial hepatectomy. These authors studied a large number of adult animals and applied statistical methods to their observations. The average weight of the liver was found to be 3.58 per cent of the body weight. They noted that the weight of the left lateral and median lobes of the liver averaged from 65 to 75 per cent of that of the entire organ. After the removal of these two lobes complete regeneration occurred by from the tenth to the fourteenth day after operation, and regeneration was most rapid on from the third to the fourth day.

Effect of Diet on Regeneration of the Liver.—The effect of diet on regeneration of the liver has been studied almost entirely in animals given hepatic poisons. Opie and Alford [5] demonstrated that a carbohydrate diet protected the liver of the rat from necrosis resulting from chloroform and phosphorous poisoning. Graham [6] was the first to show that carbohydrate prevented damage to the liver from chloroform poisoning in young dogs. It was also shown that the glycogen content of the protected liver was relatively high. Moise and Smith [8] fed rats a variety of diets and then damaged the hepatic cells by chloroform. A morphologic study of the livers of these animals showed that on the basis of resistance to toxicity a diet high in protein is better than a diet high in carbohydrate, which in turn is preferable to a stock diet. The stock diet, moreover, produces greater resistance than a diet high in fat. No report has been found dealing with the effect of diet on the regeneration of the liver after partial hepatectomy.

Effect of Diet on Glycogenesis.—The literature [9] abounds in references to the relative values of sugars, amino-acids, fats and metabolites as sources of glycogen in the liver. Greisheimer and Johnson [10] and Greisheimer [11] studied the effect of different diets on the deposition of glycogen in the liver of young rats. Their work is not pertinent to the study reported here.

Factors Affecting Concentration of Glycogen.—In recent years it has been shown that the interpretation of glycogen concentrations in

4. Higgins, G. M., and Anderson, R. M.: Experimental Pathology of the Liver, Arch. Path. **12**:186 (Aug.) 1931.

5. Opie, E. L., and Alford, L. B.: The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform, J. A. M. A. **62**:895 (March 21) 1914; J. Exper. Med. **21**:1, 1915.

6. Graham, E. A.: J. Exper. Med. **21**:185, 1915.

7. Footnote deleted by the author.

8. Moise, T. F., and Smith, A. H.: J. Exper. Med. **40**:13, 1924.

9. Cori, C. I.: Physiol. Rev. **11**:143, 1931.

10. Greisheimer, E. M., and Johnson, O.: Am. J. Physiol. **90**:369, 1929; ibid. **94**:11, 1930; J. Nutrition **3**:297, 1930.

11. Greisheimer, E. M.: J. Nutrition **4**:411, 1931.

the liver of experimental animals must be made with caution, since the methods of killing experimental animals in common use have been shown to have an effect on the concentration of hepatic glycogen. It has been shown that bleeding,[12] a blow on the head,[9] decapitation [13] and many anesthetics [14] all cause a fall in the amount of glycogen in the liver. Cori and Cori [15] and Deuel and his associates [16] stated that when amytal is given intraperitoneally in doses large enough to produce quick narcosis the the amount of glycogen in the liver is not appreciably reduced in a short period.

In addition it must be remembered that there are wide variations in the glycogen content of the liver of well fed rats taken directly from their cages.[17] In starved rats the amount of glycogen is relatively constant.[18] Furthermore, Deuel and his associates [19] stressed the importance of sex in its relationship to the concentration of glycogen in the liver. Although no differences were observed in well fed animals, starved males showed higher values for the glycogen content of the liver than did the females. Other investigators have confirmed this observation.[20]

EXPERIMENTAL PROCEDURE

Rats of Wistar stock served as experimental subjects. After being weaned they were fed a stock diet.[21] A maximum of eight animals were kept in large cages and given food and water ad libitum. When 60 days old these animals were hepatectomized or laparotomized and were immediately given either a stock diet or one high in carbohydrate, high fat, or high protein (table 1). Sixty animals of the same sex were placed on each diet.

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12. Palmer, W. W.: J. Biol. Chem. **30**:79, 1917.

13. Evans, C. L.; Tsai, C., and Young, F. G.: J. Physiol. **73**:81, 1931.

14. Evans, C. L.; Tsai, C., and Young, F. G.: J. Physiol. **73**:67, 1931. Murphy, G. E., and Young, F. G.: ibid. **76**:395, 1932.

15. Cori, C. I., and Cori, G. T.: J. Biol. Chem. **85**:275, 1929.

16. Deuel, H. J.; McKay, E. M.; Jewel, P. W.; Gulick, M., and Grunewald, C. F.: J. Biol. Chem. **101**:301, 1933.

17. Cori, C. F., and Cori, G. T.: J. Biol. Chem. **81**:389, 1929.

18. Miller, M. M., and Lewis, H. B.: J. Biol. Chem. **98**:133, 1932. Barbour, A. D.; Chaikoff, I. L.; McCleod, J., and Orr, M. D.: Am. J. Physiol. **88**:243, 1927. Cori and Cori.[17]

19. Deuel, H. J.; Gulick, M.; Grunewald, E. F., and Cutler, C. H.: J. Biol. Chem. **104**:519, 1934. Gulick, M.; Samuels, L. T., and Deuel, H. J.: ibid. **105**: 29, 1934.

20. Stöhr, R.: Ztschr. f. physiol. Chem. **212**:121, 1932; quoted in Chem. Abstr. **27**:124, 1933. Greisheimer.[11]

21. Bal-Ra (obtained from the Valentine Company, of Richmond, Va.) contains: moisture, 9.57 per cent; protein, 29.38 per cent; fat, 5.7 per cent; ash, 9.03 per cent, and carbohydrate, 46.32 per cent.

On the third, seventh, fourteenth, twenty-first and twenty-eighth days after operation eight partially hepatectomized animals, two laparotomized animals used as controls and two on which no operation was performed were killed. The rats were killed when in a well fed condition immediately after removal from the cage, with the exception of two partially hepatectomized rats that were starved for twenty-four hours.

Partial hepatectomy was done with the rats under ether anesthesia. No aseptic precautions were taken. The technic for this operation has been described by Higgins and Anderson.[4] A midline incision was made; the attachments of the left lateral and median lobes of the liver to the diaphragm were freed; a ligature was placed around the pedicle of each lobe, and the lobes were removed. The wound was closed with two layers of silk suture, one in the muscle and peritoneum and one in the skin. The operation lasted about seven minutes.

TABLE 1.—*Composition (Expressed in Percentages) of Diets Used in Experiments*

	Stock Diet*	Carbohydrate Diet	Fat Diet	Protein Diet
Protein	33.13	20‡	30‡	75‡
Fat	10.90	..	52¶	10¶
Carbohydrate	39.52	66‖	..	..
Salt	.....	4#	4#	5#
Yeast	†	6	8	6
Cod liver oil	†	4	6	4
Moisture	9.25	..	..	..
Crude fiber	2.70	..	..	..
Bone phosphate of lime	6.22	..	..	..
Ash	7.20	..	..	..

* Data relative to the stock diet were furnished by the manufacturer.
† Cod liver oil and yeast are included in the formula.
‡ Meat residue.
‖ Corn starch.
Salt mixture (Osborne and Mendell).
¶ Lard.

At the time of death the rats were given 90 mg. of sodium amytal per kilogram of body weight intraperitoneally, and within three or four minutes the abdomen was opened. Two sections of liver were removed immediately for duplicate determinations of glycogen. The animals were killed by bleeding and opening the thorax. The remainder of the liver was removed and weighed. The total weight of the liver was calculated and recorded. In a few instances blood was drawn for van den Bergh determinations.

The surface area was calculated by the formula employed by Lee:[22] $12.54 \times W^{0.6}$.

The sections of liver for the determination of glycogen were dropped into a 30 per cent solution of potassium hydroxide; they usually weighed about 0.5 Gm. The interval between the opening of the abdomen and the immersion of the tissue in potassium hydroxide was less than one minute. The glycogen content was determined by the Pflüger method as modified by Somogyi and his associates.[23] The amount of sugar was determined by the Shaffer-Hartmann procedure,[24] using reagents recently described by Shaffer.[25]

22. Lee, M. O.: Am. J. Physiol. **89**:24, 1929.

23. Goode, C. A.; Kramer, H., and Somogyi, M.: J. Biol. Chem. **100**:485, 1933.

24. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: vol. II. Methods, Baltimore, Williams & Wilkins Company, 1932.

25. Shaffer, P. A., and Somogyi, M.: J. Biol. Chem. **100**:695, 1933.

The liver and both kidneys were preserved for microscopic study and analysis of lipids. These microscopic and chemical observations will be presented as a separate study.

EXPERIMENTAL RESULTS

1. *Effect of Diet on Body Weight in the Control and the Experimental Animal.*—All the partially hepatectomized rats lost weight immediately after operation (tables 2, 3, 4 and 5). However, the ability to regain body weight was determined by the dietary regimen. The greatest increase in weight in the controls on which no operation was performed, in the laparotomized controls and in the partially hepatectomized animals was observed in the animals fed the stock and the high carbohydrate diet; the smallest gain was noted in the animals fed the high fat and the high protein diet; the laparotomized rats used as controls on the high fat diet consistently showed the smallest increment in weight.

The percentage increase of weight in the animals on the stock diet killed twenty-eight days after the beginning of the experiments was not considered because of a discrepancy in age of about fifteen days.

2. *The Effect of Diet on Ratio of the Weight of the Liver.*—The correct index to be used in estimating changes in the weight of the liver must be based on a reliable standard, such as surface area or body weight. A large liver may or may not be indicative of marked regeneration, since it is well known that the weight of this organ and of other organs is determined to a great extent by the size of the animal. Data concerned with the weight of the liver may be best interpreted by using a ratio employing the measurement of the surface area or of the body weight. On account of the increasing tendency to employ the surface area as a constant for reference, the weights of the liver in this study have been expressed in terms of the ratio of the weight of the liver to the surface area. Although the use of the surface area or the body weight in connection with the estimation of the weights of organs is customary in investigative work, it is believed that the quotients obtained in such determinations are not more than approximately accurate as a measure of the regeneration of the liver. In the first days after operation engorgement with blood to an uncertain degree creates a change in the ratio which has no significance as an index of the amount of regeneration. In the same way in the later stages the deposition of fat and glycogen and the proliferation of connective tissue and blood vessels disturb the ratio.

The weight of the liver was increased markedly during the first few days after operation. Although no attempt was made to estimate the amount of liver left at operation, gross examination of the tissue indicated marked engorgement and some increase in size by the third day. The tissue was firm and livid. Seven days after partial hepatectomy the liver was still engorged, and there was a greater increase in size. After this time the liver appeared normal in color.

(*a*) Stock Diet (table 2): The liver attained its maximum size on the twenty-first day. There was an increase in the ratio of the weight of the liver to the surface area of from 1.77 to 2.59. There was no further increase in this ratio on the twenty-eighth day.

Laparotomy alone had a marked effect on the ratios as compared to those for animals used as controls. The average ratio for the control group was large (3.12) during the earlier days and gradually decreased as the animals grew older (2.47). The differences did not manifest themselves in the laparotomized rats. However, on the twenty-eighth day the ratios were the same (2.4) in the two groups.

TABLE 2.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Male Rats on a Stock Diet*

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			$\frac{\text{Weight of Liver}}{\text{Surface Area}} \times 100$		
				Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
6	Partially hepatectomized	60	3	144	176	168	120	168	151	1.64	1.84	1.77
6	Partially hepatectomized	61	7	144	196	172	150	210	179	1.76	2.60	2.11
6	Partially hepatectomized	61	14	138	198	169	162	222	192	1.98	2.41	2.25
6	Partially hepatectomized	63	21	154	176	165	180	240	216	2.10	2.79	2.59
6	Partially hepatectomized	76	28	180	250	230	214	300	271	1.51	2.11	2.54
2	Laparotomized controls	60	3	190	192	191	190	198	194	2.57	2.72	2.58
2	Laparotomized controls	61	7	162	162	162	178	184	181	2.46	2.72	2.54
2	Laparotomized controls	61	14	132	146	139	160	182	171	2.21	2.66	2.44
2	Laparotomized controls	63	21	162	176	169	224	248	236	2.92	3.02	2.91
2	Laparotomized controls	79	28	190	210	200	214	240	227	2.36	2.54	2.46
2	Controls without operation	60	3	150	180	165	164	190	177	2.77	2.96	2.86
2	Controls without operation	61	7	162	184	173	200	218	209	3.18	3.19	3.12
2	Controls without operation	61	14	182	184	183	220	244	232	2.61	2.78	2.70
2	Controls without operation	63	21	130	150	140	170	224	197	2.35	2.86	2.57
2	Controls without operation	79	28	212	214	213	244	254	249	2.42	2.55	2.47
2	Starved partially hepatectomized	60	3	142	158	150	122	136	129	1.42	1.42	1.42
2	Starved partially hepatectomized	82	7	214	230	222	190	194	192	1.63	1.70	1.69
2	Starved partially hepatectomized	61	14	146	162	154	160	170	165	1.64	1.69	1.67
2	Starved partially hepatectomized	105	21	230	258	244	232	268	250	1.87	2.26	2.07
2	Starved partially hepatectomized	79	28	234	258	246	254	266	260	1.81	1.98	1.85

TABLE 3.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Male Rats on a High Carbohydrate Diet*

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			Weight of Liver / Surface Area × 100		
				Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
6	Partially hepatectomized	61	3	120	170	151	110	166	147	1.47	1.87	1.64
5	Partially hepatectomized	61	7	134	192	164	130	202	175	1.54	2.08	1.93
6	Partially hepatectomized	60	14	144	188	183	178	232	196	2.35	2.76	2.46
6	Partially hepatectomized	60	21	114	172	152	154	232	201	1.82	2.15	1.94
6	Partially hepatectomized	61	28	162	178	169	224	248	235	2.21	2.91	2.42
2	Laparotomized controls	61	3	138	144	141	140	158	149	2.30	2.33	2.26
2	Laparotomized controls	61	7	142	154	148	142	178	160	2.18	2.32	2.25
2	Laparotomized controls	60	14	134	166	150	162	208	185	2.06	2.72	2.50
2	Laparotomized controls	60	21	110	150	130	132	182	157	1.90	2.07	1.92
2	Laparotomized controls	61	28	156	180	168	220	278	247	2.45	2.87	2.68
2	Controls without operation	61	3	170	222	196	176	210	193	2.46	3.19	2.78
2	Controls without operation	61	7	176	210	193	198	248	223	2.42	2.91	2.69
2	Controls without operation	60	14	190	214	202	232	232	232	2.27	2.84	2.50
2	Controls withous operation	60	21	160	172	166	202	236	219	2.35	2.91	2.58
2	Controls without operation	61	28	152	156	154	234	250	242	2.30	2.62	2.46
2	Starved partially hepatectomized	61	3	132	178	155	118	152	135	1.59	1.87	1.70
2	Starved partially hepatectomized	61	7	180	182	181	160	168	164	1.44	1.61	1.53
2	Starved partially hepatectomized	60	14	130	166	148	120	154	137	1.55	1.60	1.54
2	Starved partially hepatectomized	60	21	180	198	189	180	226	203	1.77	1.95	1.83
2	Starved partially hepatectomized	61	28	166	174	170	226	248	237	1.89	2.01	1.95

TABLE 4.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Female Rats on a High Fat Diet*

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			$\frac{\text{Weight of Liver}}{\text{Surface Area}} \times 100$		
				Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
6	Partially hepatectomized	64	3	118	146	130	110	142	125	1.53	2.25	1.93
6	Partially hepatectomized	64	7	114	140	127	114	150	131	2.06	2.38	2.08
6	Partially hepatectomized	67	14	118	134	127	132	154	143	1.86	2.31	2.00
6	Partially hepatectomized	62	21	114	130	122	132	150	142	2.18	2.44	2.31
5	Partially hepatectomized	62	28	108	148	128	140	188	168	2.30	2.48	2.27
2	Laparotomized controls	64	3	136	156	146	138	164	151	2.39	2.44	2.36
2	Laparotomized controls	64	7	120	124	122	128	144	136	2.15	2.23	2.14
2	Laparotomized controls	67	14	130	132	131	142	154	148	2.08	2.08	2.07
2	Laparotomized controls	62	21	116	122	119	144	156	150	2.21	3.30	2.30
2	Laparotomized controls	62	28	112	124	118	152	174	163	2.19	2.33	2.26
2	Controls without operation	64	3	114	132	123	124	138	131	2.08	2.59	2.29
2	Controls without optration	64	7	122	132	127	136	142	139	2.23	2.26	2.17
2	Controls without operation	67	14	106	132	119	136	162	149	2.12	2.28	2.20
2	Controls without operation	62	21	124	130	127	124	144	134	2.21	2.22	2.22
2	Controls without operation	62	28	120	132	126	158	182	170	2.34	2.71	2.53
2	Starved partially hepatectomized	64	3	124	156	140	110	140	125	1.65	1.85	1.72
2	Starved partially hepatectomized	64	7	128	132	130	114	122	118	2.29	2.40	2.30
2	Starved partially hepatectomized	67	14	114	124	119	112	128	120	1.63	1.73	1.68
2	Starved partially hepatectomized	62	21	120	122	121	132	146	139	2.11	2.29	1.97
2	Starved partially hepatectomized	62	28	116	120	118	122	140	131	1.77	1.96	1.90

In the starved partially hepatectomized rats the ratios were lower than in the corresponding groups of well fed animals. They varied from an average of 1.42 on the third day to 2.07 on the twenty-first day.

(*b*) High Carbohydrate Diet (table 3): The ratios of the weight of the liver to the surface area in the hepatectomized animals on this diet reached their maximum value (average, 2.46) on the fourteenth day. The lower ratios obtained on the twenty-first day were undoubtedly due to the absence of sufficient food in the cage before death, which was indicated by the empty stomachs of the rats when killed. The average of the values obtained on the twenty-eighth day was slightly lower than the maximum ratio (2.42).

The effect of laparotomy on the ratio was shown on the third and seventh days of the experiment; for example, the values were 2.26 and 2.25 for the laparotomized rats, as compared with 2.78 and 2.69, respectively, for the animals used as controls. The ratios for the laparotomized rats on the twenty-first day were low because of insufficient food in the cage.

In the starved partially hepatectomized rats the ratios were about the same on the third, seventh and fourteenth days.

(*c*) High Fat Diet (table 4): The ratios of the weight of the liver to the surface area in the partially hepatectomized animals remained unusually constant throughout the entire period of the experiment, despite the marked deposition of fat in the liver. The greatest variations in the average ratios were from 1.93 to 2.31, the smallest value being obtained on the third day and the maximum on the twenty-first day. There was practically no difference in the ratios for the control rats on which no operation was performed and the laparotomized control rats.

The results of starvation in the partially hepatectomized rats are difficult to interpret, since the ratios on the seventh day were higher than those of the animals of the corresponding age which were fed. Furthermore, the ratios were not as low as those noted for the animals on the standard and high carbohydrate diets on which a similar hepatectomy was done.

(*d*) High Protein Diet (table 5): The ratios for the partially hepatectomized rats were extremely constant throughout the experiment, with maximum variations between 1.91 and 2.31.

The difference in the effect of laparotomy noted in the animals on a stock diet and on a high carbohydrate diet was not evident in the rats on the high protein diet.

The effect of starvation was rather marked. It may be said that the ratios apparently decreased more markedly in these rats than in any group studied.

Effect of Diet on the Glycogen of the Liver of Control Rats on Which No Operation Was Performed and of Partially Hepatectomized Rats (table 6).—Since engorgement of the liver of the partially hepatectomized rats occurred during the first two periods of this experiment, any interpretation of percentage values cannot be seriously considered. Therefore, the total number of grams of glycogen in the liver was also considered in order to estimate the deposition of this material.

(*a*) Stock Diet: The percentage concentration of the glycogen of the liver of the control rats without operation decreased with the age of the animal. Despite the uniformity of the results obtained with the two animals in each group used as controls, these values are open to criticism, owing to the small number of rats. The results obtained for the laparotomized rats used as controls tended to be uniform. The effect of this operation again manifests itself in a lower and more constant glycogen concentration in the liver.

TABLE 5.—*Relationship of the Weight of the Liver to the Surface Area in Partially Hepatectomized and in Control Female Rats on a High Protein Diet*

No. of Animals	Type of Animals	Age at Operation, Days	Interval After Operation, Days	Body Weight Before Operation, Gm.			Body Weight at Death, Gm.			$\frac{\text{Weight of Liver}}{\text{Surface Area}} \times 100$		
				Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
6	Partially hepatectomized	66	3	104	126	117	100	124	113	1.83	2.06	1.91
6	Partially hepatectomized	59	7	114	154	127	118	134	126	1.77	2.82	2.24
5	Partially hepatectomized	64	14	112	134	125	118	134	130	2.22	2.37	2.26
6	Partially hepatectomized	66	21	116	142	123	118	162	143	2.17	2.38	2.31
6	Partially hepatectomized	60	28	102	122	113	122	146	134	2.02	2.38	2.27
2	Laparotomized controls	66	3	94	126	110	98	130	116	2.20	2.50	2.36
2	Laparotomized controls	59	7	120	122	121	126	130	128	2.35	2.46	2.42
2	Laparotomized controls	64	14	116	148	132	142	168	155	2.53	2.85	2.69
2	Laparotomized controls	66	21	122	142	132	144	150	147	2.43	2.51	2.47
2	Laparotomized controls	60	28	108	126	117	134	142	138	2.27	2.41	2.34
2	Controls with no operation	66	3	120	132	126	122	134	128	2.43	2.50	2.46
2	Controls with no operation	59	7	114	130	122	124	140	132	2.33	2.34	2.34
2	Controls with no operation	64	14	144	150	147	152	168	160	2.24	2.62	2.49
2	Controls with no operation	66	21	142	170	156	158	180	169	2.34	2.62	2.46
Lost	Controls with no operation	60	28	...	...	...	...	...	...	....	....	....
2	Starved partially hepatectomized	66	3	104	120	112	90	110	100	1.16	1.68	1.40
2	Starved partially hepatectomized	59	7	112	120	116	96	108	102	1.48	1.51	1.50
2	Starved partially hepatectomized	64	14	116	130	123	120	126	123	1.49	1.56	1.53
2	Starved partially hepatectomized	66	21	126	140	133	122	130	126	1.78	1.83	1.80
2	Starved partially hepatectomized	60	28	126	140	133	134	146	140	1.63	1.77	1.78

TABLE 6.—*Average Values for Glycogen in Well Fed Partially Hepatectomized and in Control Rats*

Days After Operation	No. of Animals	Type of Animal	Stock Diet, Males: Glycogen, per Cent: Minimum	Stock Diet, Males: Glycogen, per Cent: Maximum	Stock Diet, Males: Glycogen, per Cent: Average	Stock Diet, Males: Total Content of Liver, Gm.	High Carbohydrate Diet, Males: Glycogen, per Cent: Minimum	High Carbohydrate Diet, Males: Glycogen, per Cent: Maximum	High Carbohydrate Diet, Males: Glycogen, per Cent: Average	High Carbohydrate Diet, Males: Total Content of Liver, Gm.	High Fat Diet, Females: Glycogen, per Cent: Minimum	High Fat Diet, Females: Glycogen, per Cent: Maximum	High Fat Diet, Females: Glycogen, per Cent: Average	High Fat Diet, Females: Total Content of Liver, Gm.	High Protein Diet, Females: Glycogen, per Cent: Minimum	High Protein Diet, Females: Glycogen, per Cent: Maximum	High Protein Diet, Females: Glycogen, per Cent: Average	High Protein Diet, Females: Total Content of Liver, Gm.
3	6	Partially hepatectomized.....	0.28	1.19	0.60	0.028	1.09	2.61	1.85	0.079	0.03	0.39	0.16	0.007	0.30	0.60	0.43	0.018
7	6	Partially hepatectomized.....	0.52	1.87	1.22	0.048	2.21	3.03	2.56**	0.137	0.91	1.63	1.28	0.064	0.62	2.93	1.68	0.086
14	6	Partially hepatectomized.....	1.58	2.55	2.08	0.137	3.63	4.53	3.97	0.290	0.99	1.94	1.33	0.065	1.66	2.59	2.25*	0.118
21	6	Partially hepatectomized.....	1.30	2.54	2.28	0.109	1.49*	2.32*	1.99*	0.117*	1.52	2.31	1.94	0.109	0.66	2.20	1.41	0.080
28	6	Partially hepatectomized.....	1.01	2.35	1.80	0.165	1.66	3.34	2.20	0.176	1.31	1.64	1.33**	0.082	1.09	2.30	1.65	0.088
3	2	Laparotomized controls.....	0.83	1.09	0.91*	0.071	2.57	3.58	3.07	0.176	0.89	1.43	1.66	0.099	1.76	2.06	1.91	0.097
7	2	Laparotomized controls.....	1.59	3.68	2.63	0.189	2.90	3.96	3.43	0.186	1.74	1.77	1.75	0.089	1.78	2.45	2.11	0.117
14	2	Laparotomized controls.....	2.46	3.17	2.81	0.189	3.28	3.83	3.55	0.255	1.24	1.36	1.30	0.067	2.12	2.27	2.20	0.153
21	2	Laparotomized controls.....	2.11	2.53	2.32	0.224	0.70*	1.87*	1.28*	0.064	1.40	1.63	1.51	0.088	2.13	2.20	2.17	0.134
28	2	Laparotomized controls.....	2.46	2.61	2.53	0.202	3.33	3.34	3.34	0.306	1.23	1.26	1.24	0.079	1.98	2.00	1.99	0.112
3	2	Controls without operation....	3.20	3.40	3.30	0.264	2.38	2.67	2.52	0.207	0.86	1.49	1.17	0.063	2.31	2.48	2.40	0.136
7	2	Controls without operation....	3.80	4.39	4.09	0.405	2.38	3.37	2.82	0.245	1.10	2.04	1.57	0.083	2.15	3.15	2.65	0.145
14	2	Controls without operation....	2.60	3.16	2.88	0.256	2.02	2.62	2.32	0.191	1.62	1.71	1.66	0.092	1.30	2.21	1.75	0.113
21	2	Controls without operation....	2.35	2.80	2.57	0.197	2.92	2.97	2.95	0.243	1.25	1.49	1.37	0.072	1.86	1.85	1.80	0.121
28	2	Controls without operation....	1.02	1.63	1.33	0.113	3.47	4.30	3.88	0.323	1.78	2.41	2.09	0.145	+	+	+	+

* The stomach was empty at the time of death, representing unintentional starvation.
** Five animals are represented by this value.
\+ Lost

The total amount of glycogen in the liver of the partially hepatectomized rat gradually increased from an average minimum amount of 0.028 Gm. on the third day to a maximum of 0.169 Gm. on the twenty-first day. It will be noted that this maximum value did not approach the minimum value of 0.189 Gm. (at the end of seven days) for the laparotomized control animals.

(*b*) High Carbohydrate Diet: There was a definite difference in the glycogen concentrations for control rats on which no operation was performed and the laparotomized control rats. Despite the higher percentage concentration in many of the laparotomized animals, the absolute amount present was smaller in many cases, owing to the smaller livers. The number of grams of glycogen deposited was definitely low in the laparotomized rats killed on the third and seventh days after operation.

The average absolute amount of glycogen in the partially hepatectomized rats increased from 0.079 Gm. on the third day to 0.29 Gm. on the fourteenth day and decreased to 0.176 Gm. on the twenty-eighth day. The highest glycogen concentration (0.079 Gm.) on the third day after operation was seen in rats on this diet. The average maximum value of 0.29 Gm. of glycogen was almost as high as the largest amount deposited in the liver of laparotomized control rats (0.306 Gm.).

The absence of sufficient food and its effect on the glycogen of the liver are markedly demonstrated in these animals. A short period of no ingestion of food resulted in a precipitous drop in the values for glycogen.

(*c*) High Fat Diet: The lowest percentage and absolute values for glycogen in the entire series of control rats on which no operation was performed and of laparotomized control animals were noted in the control animals fed this diet. Laparotomy has no apparent effect on the values for the glycogen of the liver.

The partially hepatectomized rats also presented exceedingly low values. On the third day after operation there was an almost complete absence of glycogen (0.007 Gm., or 0.16 per cent). The average maximum values of 1.94 per cent and 0.109 Gm. of glycogen were noted on the twenty-first day and were higher than the concentrations for the corresponding control groups.

(*d*) High Protein Diet: The average values for glycogen for these control animals were somewhat variable. They were relatively low but were definitely higher than those for the rats on the high fat diet.

The values for glycogen for the partially hepatectomized rats were extremely low. The average absolute values increased from 0.018 Gm. on the third day to a maximum of 0.118 Gm. on the fourteenth day. There was a decrease to 0.08 and 0.088 Gm. on the twenty-first and twenty-eighth days, respectively. During these later days the values for glycogen were about the same as those noted for the animals on the high fat diet during a similar experimental period.

Effect of Starvation on Concentration of Glycogen in Partially Hepatectomized Rats.—The lowest average percentage and absolute values were observed after starvation in the animals previously fed the high carbohydrate diet. This is further emphasized by the fact that the carbohydrate-fed animals were males. It has been pointed out that starving males have higher values for glycogen than females. The starving females on the high fat and protein diets had the highest glycogen concentrations. This discrepancy in the glycogen content of the liver of rats on various diets is marked and must therefore have physiologic significance.

COMMENT

In order to discuss possible practical applications of the data obtained from this study it is essential first to express in condensed form the results of these experiments.

The feeding of a well balanced stock ration was accompanied by the most rapid gain in weight in both the control and the experimental groups. The hepatectomized animals were able to regain their lost weight rapidly; on the twenty-first day they weighed approximately as much as the rats on which simple laparotomy had been performed. The animals on a high carbohydrate diet showed almost as satisfactory a gain in body weight. The animals on the high protein and high fat diets showed a considerably smaller gain in weight than those in either of the other two groups.

Under the conditions of these experiments the highest values for glycogen in the liver of the partially hepatectomized animals were seen also in the animals on the high carbohydrate diet and in those on the stock diet. Storage of glycogen in the rats fed on high protein and high fat diets was minimal.

One of the most striking observations was the effect of the previous diet on the glycogen concentration in the liver of animals starved for twenty-four hours. The lowest values for glycogen observed in the entire series of experiments were obtained in the rats which had been on the high carbohydrate diet, the livers of which were presumably richest in glycogen prior to starvation. It is particularly interesting that even a short period of starvation had the same effect, as shown by the fact that very low values for glycogen in the liver were observed in all the animals in which the stomach was empty at the time of death in spite of the usual feeding on the preceding day (table 6). It is believed that this effect is the result of an excess production of insulin called forth by the previous high intake of carbohydrate.

It is, of course, not known how directly the observations made in these experiments can be carried over to the clinical field and be applied to patients with livers damaged by inflammatory, neoplastic or degenerative processes. The effect of diet on the patient with a damaged liver is of great importance, and there is need for further and more accurate knowledge which can be applied clinically. It is generally believed by clinicians that a high carbohydrate diet is desirable for the patient with a presumably damaged liver, on the basis that the glycogen concentration of the liver should be kept high, a belief summarized by the rather indefinite phrase "protecting the damaged liver." The impression that patients with hepatic disease do better on a high carbohydrate diet is substantiated by repeated clinical experience. Experimental evidence, such as has already been cited in relation to poisonings, etc., has given weight to this conclusion without necessarily explaining the mechanism. If the type of damage to the liver created in these experiments is at all comparable to other types of damage the results of the present study offer further support to the clinical point of view. Certainly, the effect of either the carbohydrate or the stock diet (the second of which may

be compared to a well balanced hospital diet) was more favorable on the experimental animals in regard both to storage of glycogen and to gain in body weight than was either the high fat or the high protein diet.

A second generalization is perhaps also applicable to the patient. The sharp decrease in the glycogen content of the liver after twenty-four hours or less of starvation of the animals fed a high carbohydrate or stock diet may possibly point a clinical moral. For example, it is customary to prepare patients suffering from severe inflammation of the gallbladder for operation by increasing the carbohydrate intake both by mouth and intravenously with the idea of increasing the amount of glycogen in the liver. A fall in the mortality rate in cases of surgical treatment of the gallbladder has certainly followed the general adoption of this procedure. These experiments suggest that an increase in

TABLE 7.—*Values for Glycogen in Partially Hepatectomized Rats Starved for Twenty-Four Hours Before Death*

		Stock Diet, Males				High Carbohydrate Diet, Males				High Fat Diet, Females				High Protein Diet, Females			
		Glycogen, per Cent				Glycogen, per Cent				Glycogen, per Cent				Glycogen, per Cent			
No. of Animals	Interval After Operation Days	Minimum	Maximum	Average	Total Glycogen, Gm.	Minimum	Maximum	Average	Total Glycogen, Gm.	Minimum	Maximum	Average	Total Glycogen, Gm.	Minimum	Maximum	Average	Total Glycogen, Gm.
2	3	0.10	0.37	0.28	0.009	0.09	0.25	0.17	0.007	0.05	0.16	0.10	0.003	0.04	0.07	0.05	0.001
2	7	0.17	0.18	0.17	0.008	0.03	0.06	0.04	0.002	0.23	0.49	0.36	0.018	0.68	0.88	0.78	0.025
2	14	0.11	0.18	0.15	0.007	0.27	0.49	0.38	0.014	0.53	0.58	0.55	0.021	0.24	0.76	0.50	0.017
2	21	0.37	0.48	0.42	0.030	0.17	0.33	0.25	0.014	0.70	0.90	0.80	0.038	0.84	0.89	0.87	0.036
2	28	0.46	0.76	0.61	0.039	0.05	0.18	0.11	0.007	0.38	0.93	0.62	0.027	0.11	0.47	0.28	0.016

carbohydrate intake should be continued actively throughout the preoperative and immediate postoperative periods. They show that carbohydrate starvation after a diet rich in carbohydrates results in a lower value for the glycogen of the liver than does starvation of the animals to which a lower amount of carbohydrate has been given. In other words, the patient with a damaged liver who undergoes operation should have a continued high carbohydrate intake throughout the critical period. That it is perhaps justifiable to apply these experimental results clinically is suggested by certain preliminary observations on the glycogen of the liver of surgical patients.[26]

SUMMARY

A series of rats subjected to partial hepatectomy were compared with control animals, both rats on which no operation was performed and rats subjected to simple laparotomy. These animals were maintained on (1) a well balanced diet, (2) a high carbohydrate diet. (3) a

26. Unpublished results.

high fat diet and (4) a high protein diet. The weight of the animal, the ratio of the weight of the liver to the surface area and the values for glycogen in the liver were determined for all the animals.

Partially hepatectomized rats fed a well balanced diet regain their normal weight twenty-one days after operation. On the carbohydrate diet these animals grow rapidly but do not reach the level of the control animals. The smallest gain in weight is seen in the animals on high fat and high protein diets.

The remnant of liver increases in weight in all the rats, as judged by the ratio of the weight of the liver to the surface area. The greatest increase in the weight of the liver is noticed in the rats on the well balanced and carbohydrate diets. The significance of this ratio has been discussed.

The highest values for glycogen in the liver in the partially hepatectomized rats are seen in the rats fed on high carbohydrate and stock diets.

Glycogen in the liver is reduced to the greatest degree by starvation of the animals which have been on a high carbohydrate diet.

If one can carry over into the clinic experimental observations made on animals subjected to partial hepatectomy, one must conclude that (*a*) a well balanced or a high carbohydrate diet will best maintain the patient suffering from a damaged liver and (*b*) sudden starvation in patients previously furnished a rich carbohydrate intake must be avoided on account of the serious depletion of glycogen in the liver which immediately follows cessation of carbohydrate intake.